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OCTOBER, 1932

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, July 10, 1925, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized July 29, 1920.

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ARCHIVES OF SURGERY

VOLUME 25 OCTOBER, 1932 NUMBER 4

THE PROCESS OF TENDON REPAIR

AN EXPERIMENTAL STUDY OF TENDON SUTURE AND TENDON GRAFT

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The process of tendon repair and the technic of tendon suture and tendon graft are two of the major problems of present day surgery. The thirty-eighth session of the French Congress of Surgery, 1929, devoted considerable time to the report of Bonnet and Bloch on the repair of tendons of the hand. This, in fact, was one of the three main subjects discussed, the other two being surgical intervention in

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Dr. Mason worked under a surgical fellowship granted by a friend who desires to remain unknown.

pulmonary tuberculosis and in Pott's disease. Despite many excellent experimental and clinical studies, there is little unity of opinion among qualified students regarding any of the major issues of the problem. The actual histologic process of the repair of divided tendons and of the healing of tendon grafts, the source of the tissues that make for union between tendon stumps and between stumps and tendon graft, has been, and still is, the subject of considerable controversy. The question of spontaneous repair is by no means obviously explicable, and its experimental study has led to several logical conceptions. The significance of the synovial sheath in the process of repair led to a controversy between Bier and his pupils and Rehn and his pupils which is still being waged. The scanty vascular supply of tendon tissue and the necessity of a good vascular supply to reparative tissue are two factors that appear to be constantly working against the surgeon. The force of this fact is more strongly brought out when it is remembered that adequate vascularization of grafted tissues, e. g., a skin graft, requires rest and immobilization, while rest and immobilization of injured tendons favor the formation of adhesions—the most important factor making for the failure of operations on tendons. Experimental and clinical observations have shown that function is of major importance in determining the histologic structure of tendon tissue, and emphasize the necessity for purposeful movements of tendons during the course of healing. The necessity of function during healing would seem also to be incompatible with the immobilization necessary to obtain efficient vascularization and secure union. The tension at which tendon should be sutured is a very definite and perplexing problem. While there is no doubt that freshly divided tendon should be sutured end-to-end, after relaxation has been obtained by bringing origin and insertion of the muscle as closely together as possible (Mayer), the problem is not so simple when one considers suture and repair of older injuries. Here the retraction is due not only to muscular tonus, but to intramuscular fibrosis as well, and while the former may be overcome, the latter is to a certain extent permanent, and end-to-end suture leads to permanent shortening of the tendon.

At the suggestion of Dr. Allen B. Kanavel, a series of studies of tendon surgery have been undertaken in the laboratory of experimental surgery of Northwestern University School of Medicine. Under Dr. Kanavel's guidance, it has been planned to study various aspects of the problem in an attempt to obtain, experimentally, first hand knowledge of tendon repair. The present report deals with a histologic study of healing tendons and tendon grafts.

HISTORICAL DATA

It is not surprising to one acquainted with tendon surgery that operative procedures on these structures found slight general favor

with the surgical profession until after the advent of antiseptic surgery. The ancient and medieval surgeons were handicapped not only by the lack of knowledge of wound infection, but also by the fact that it was not until the middle of the eighteenth century that clear distinction was made between tendon and nerve, despite the fact that Galen had described the differential anatomy of tendons, nerves and ligaments. Without doubt, the catastrophic possibilities of this lack of knowledge were enough to discredit most of the early operative repair of tendon wounds. There must have been many lacerating injuries of the hands and feet with which the older surgeons had to deal; still reports of tendon repair are meager and scattered.

Galen in the second century demonstrated the differential anatomy of tendons, nerves and ligaments, but warned against the ill results of tendon suture. This warning came from the fact that he considered tendon a mixture of nerve and ligament, and he considered that suture within nerve substance was likely to be followed by severe pain, twitchings and convulsions. It is not improbable that Galen had seen patients with median nerve injury at the wrist in whom the distinction between nerves and tendons had not been made and in whom suture was followed by symptoms of nerve irritation. Galen's influence was felt for nearly sixteen centuries.

The time between Galen and Haller, who demonstrated the specificity of tendon tissue, was not entirely barren. Avicenna in the tenth century strongly advocated tendon suture. It was somewhat over two hundred years later that the teachings of this Arabian physician were promulgated in Italy by Roger, Roland, Lanfranchi and William of Falicet. The last surgeon asserted that nature was unable to unite divided tendons, and that the surgeon could bring the stumps together better than nature. About the same time (early in the fourteenth century) the French surgeon, Guy de Chauliac, evidently under the influence of the Italian surgeons, attempted with but a modicum of success to defend the closure of tendon wounds.

Another two centuries elapsed before one reads in the works of Ambroise Paré in the sixteenth century of successful instances of tendon suture, and it is logical to assume that he himself had practiced it. Still there was no general acceptance of surgical procedures on tendons. The great Galen had said fourteen hundred years before that a prick of a nerve or tendon would lead to convulsions, and, without attempting experimental confirmation of this opinion, the surgical profession accepted this dictum as a fact.

During the seventeenth century a few experimenters reported successful tendon sutures on dogs. Lanzweerde divided the tendon achillis in dogs and sutured it. Healing occurred and full functional use of the leg returned. Nuck also made some experimental sutures with success.

Meekren (1682), nearly seventy-five years before Haller, tested crudely the sensitivity of tendon tissue to injury. He found no evidence that the tendons were sensitive or that the pricking or injuring of them caused pain. In the domain of clinical surgical intervention, however, tenorrhaphy was still in disrepute. The maxim never to pass a needle through a tendon had such a great hold on the profession that one surgeon (Bienaise, in dealing with a wound in the palm), instead of suturing, wrapped the suture around each end of the divided tendon and then tied the sutures together. (Curiously enough, in the case reported a good result was obtained.)[1]

It was not until after Haller in the middle of the eighteenth century, demonstrated that tendons were insensible, that operative procedures on them were to become generally accepted. Even then it took nearly two generations finally to eradicate the teachings of Galen, and it remained for Strohmeyer and Dieffenbach (1831) really to popularize the rather simple operation of tenotomy for clubfoot.

The actual process of tendon repair, in which we are particularly interested at present, was apparently first studied experimentally in dogs by Hunter in 1767. According to Hunter, tendon heals by the formation of callus, produced in much the same manner as is bone callus. V. Ammon, in 1837, considered that the defect left by tendon injuries was first filled by a formless exudate, and that later the tendon stumps themselves regenerated the new tendon. Bouvier and Velpeau, on the other hand, considered that the new tissue owed its origin mainly to the sheath tissues about the tendon. Paget noted that the tendon defect was first filled with a fluid exudate; this was then replaced by fibrous tissue which gradually took on the appearance of tendon.

It was the significance of the fluid exudate (blood) that first attracted the attention of Pirogoff. According to him, the blood exudate was the *conditio sine qua non* for tendon repair; it not only stimulated the surrounding tissues, but furnished some of the material for the new tendon. Without the exudate an incomplete scar and no, or poor, union occurs. With the exudate the regeneration is good. The material for the formation of the new tendon comes not only from the exudate, but mainly from the sheath tissues about the tendon and to a slight extent from the tendon stumps themselves. Bouvier agreed with Pirogoff, as did also Thierfelder, Boner, Feltz and Dembowski after experimental studies. Billroth, however, asserted that the exudate in reality hindered growth of the scar, in that absorption must take place and thus delay the union. Billroth's position was strongly supported by Adams, whose experimental work is not widely known. The question of the value of this exudate and the part it plays appear even in later studies of tendon

1. The preceding historical résumé was found in an editorial by an unknown writer which appeared in M. J. & Rec. **127**:156 and 213, 1928.

repair. Thus one finds that Viering in an excellent experimental paper asserted that without exudate regeneration does not occur. Other writers mention the exudate, though the view taken is that while it hinders healing, its value, in the main, is that of keeping open the defect so that regeneration can take place.

Dembowski believed that the new tendon was formed by cells that wandered into the defect from the blood. He based his conclusions on the observation that cells in the new tendon contained a dye that had been previously injected into the blood stream.

Bizzozero asserted that the new tendon was formed by the connective tissues that surrounded the stumps and that the sheath and stumps played only a minor rôle.

Güterbock partially divided tendons and found that the defect was first filled by a bit of the sheath falling into it. At the end of twenty-four hours, proliferative changes were noted in the sheath and surrounding connective tissue. The sheath played the greater rôle. By the end of three days these defects were entirely healed, and after the first week the number of mitoses was already fewer, and after several weeks the cell content was much reduced. Although the tendon played no rôle, or a very minor one, in this process, Güterbock did find proliferative changes among the tendon cells themselves, following the irritation caused by drawing a thread through the tendon.

According to Beltzow, the tendon stumps take some part in the new formation of tendon and in the organization of the scar. The intervening tissue between the stumps, however, is essentially a scar, since it tends to retract. Despite the marked histologic resemblance to tendon, the new tissue is not a true regeneration.

Viering believed, after an experimental study in which he used the tendo achillis of the rabbit, that the peritendinous and intratendinous connective tissues were the main sources of material for the organization of the tendon scar. Tendon cell mitoses were seen to be present, but not until the fourth day, and it was assumed that their participation in the process was of minor importance. Viering was the first to note that under the influence of function the nuclei and fibers of the tendon line up in rows parallel to the line of pull, while if this functional stimulus is absent, the new tissue remains disorderly and nonoriented.

Busse agreed in the main with Viering. He said that the blood exudate was gradually replaced by granulation tissue which must come from the peritenonium externum and internum. He found also that the tendon cells proliferated, but only later and in a disorderly fashion, entirely dependent on an increased vascularity, and that as the vessels diminished in number, the mitoses disappeared.

Enderlen's study of the reparative changes in the tendo achillis of the guinea-pig demonstrated the importance of the tendon cells them-

selves in the regenerative process. He showed that healing of the tendon wound is due to proliferative changes on the part of the tendon, of the peritenonium internum and externum and to some extent of the surrounding connective tissue. At first, there is a blood exudate in the gap, and the peritenonium externum falls into the wound. Some degenerative changes are seen in the ends of the stumps, i. e., swelling of the fibers, breaking up of the nuclei and leukocytic infiltration. By the second day, regenerative changes appear; mitoses are found in the tendon in great number, as well as in the internal and external peritenonium. These tendon mitoses are not dependent on proximity to blood vessels, but are frequently seen at some distance from the vessels. Some connective tissue cells, many in process of mitosis, are present in the blood exudate. By the fourth day proliferating tendon cells are found pushing into the defect, and by the sixth day tendon fibrils appear among the nuclei and form with such rapidity that by the ninth day union of the stumps is effected. These fibrils at first are arranged without any order, but as union progresses and the pull of the gastrocnemius makes itself felt, they become more and more oriented in parallel rows along the line of tendon pull. A point that Enderlen makes and that is later emphasized by Borst and is noted also in our study is that the proliferation of tendon occurs fairly generally throughout the stumps and is not confined to a narrow zone at the line of division. After the fifteenth day, Enderlen noted that the proliferation slows up, and that as time goes on the number of nuclei and vessels diminish, the fibrils become oriented in longitudinal parallel rows and the new tissue takes on the appearance of normal tendon from which it can be differentiated with difficulty.

Marchand reviewed Enderlen's actual microscopic sections and came to a somewhat different opinion as to the nature of the process. According to this pathologist, most of the new tissue came from the sheath and surrounding connective tissue. At first the proliferating tissue is definitely demarcated from the stumps, but it soon pushes into the ends of the stumps, and it is difficult, probably impossible, to distinguish between tendon cell mitoses and connective tissue cell mitoses. Marchand did not deny that the tendon cells proliferated, but he did not believe that they took an important part in the process of tendon repair. The early irregular arrangement of the tissues filling the defect spoke for its varied origin. Marchand did say, however, that it made no great difference whence the tissue came, since it eventually produced a structure functionally equivalent to tendon.

Schradick believed that normal tendon does not form in a tendon defect, but that this is filled by connective tissue brought in by the surrounding tissues following retraction of the stumps. Although he noted mitoses of tendon cells, he considered them to be due to hyperemia

and not to any particular regenerative power on the part of the tendon. The new tendon, he noted, gradually became oriented and arranged in a long, rounded strand resembling normal tendon.

Seggel studied tendon suture experimentally in guinea-pigs and concluded that the sheath with surrounding connective tissues and the tendon took part in the process of healing. At first the gap left by division of the tendon is filled by a blood exudate, while some slight degeneration occurs in the traumatized ends of the stumps. The blood exudate is soon organized by connective tissue coming in from about the stumps and from the interstitial tissues of the tendon stumps. By the fifth day, the tendon has become hyperemic and mitoses appear first on the cut ends, and by the sixth day within the substance of the tendon at some distance from the divided ends. The gap is first filled by granulation tissue which is soon infiltrated by the proliferating tendon cells that gradually replace the connective tissue. By the twenty-ninth day, continuity is completely restored, and from then on the number of nuclei diminish, so that by from the seventieth to the eightieth day the tendon looks very much like normal tendon.

Borst's exhaustive and critical study of tendon regeneration substantiates Enderlen's views. Borst showed that the scar that fills the defect comes from several sources: the tendon, the peritenonium internum and externum and the surrounding connective tissues. The blood exudate in the gap is first infiltrated by polymorphonuclear leukocytes, later by fibroblasts and by the fourth day by proliferating tendon cells. From the fourth day on, Borst found that the course of healing varies and that the evaluation of the parts played by the various elements entering into the process was quite difficult. He stated that the factors on which the further course of healing depends are numerous and vary within wide limits. Thus the nature of the operative procedure, the presence of chemical irritants, infection, suture material, etc., influenced the healing process. Borst studied with especial care the tendon nuclei and chromosomes, and believed that he was able to distinguish proliferating tendon cells from connective tissue cells, and stated that even though ordinary scar may come to resemble tendon very much, the distinction can be made.

Following the time of Borst, the attention of investigators has been directed especially toward two aspects of the problem. One of these is the question of the importance of function in the healing of tendons, and the other is the significance of the sheath in the process. Barfurth, Solger and Roux had noted the importance of stress and pull on the formation of a tendon or tendon-like tissue following tendon division, and maintained that they were important factors in tendon regeneration. Ribbert, on the other hand, asserted that function played a minor part,

that each tissue had the innate power to reproduce itself and that, regardless of function or tension, tendon proliferation resulted in the production of tendon.

This question of the effect of function on tissues led to considerable experimental study of grafts in tendon defects. Kirschner made an experimental study of autoplastic tendon and fascial grafts and found that tendon, whether subjected to function or not, remained alive, at least partly, but tended to lose its orderly parallel structure. He found that fascia also remained alive and that if subject to function, took on the character of tendon. Kirschner's experiments were corroborated by numerous others, among whom may be mentioned Ritterhaus, Dawis, Chiari, Denk, etc.

Rehn carried the experiments further and studied the effect of transplantation on all sorts of tissues grafted into tendon defects or into other places where they were or were not subjected to function. Rehn demonstrated that a tendon graft without function underwent retrogressive changes and practically disappeared, while, if subjected to function and placed under tension, not only did the graft remain viable, but it became attached in its location and replaced efficiently the lost tissue. He showed that success in the grafting of tendons depended on preservation of the external peritenonium, since this gives rise to the tissues that welded the grafts and stumps together, and, since it is less highly specialized and of a less dense structure, makes vascular connections more easily with surrounding tissues and maintains viability of the graft. Rehn experimented also in the grafting of nonspecific tissue into tendon defects and into other locations in which they were subjected to pull and stress. He found that these tissues took on tendon-like character and concluded that there was a metaplasia into tendon. Later, he modified somewhat his original conception of a true metaplasia, though he did show that the tissue very strongly resembled tendon. It was stated in objection to Rehn's conclusions as to the value of function that, since casts were applied to the part after tendon transplantation, there was no functional stimulus, and that regeneration was due to the inherent regenerative powers of the stumps. Rehn showed, however, that even under a cast the immobilized muscles were still active, and that they showed movements which acted as a functional stimulus on the graft.

The presence of a synovial sheath about a tendon may modify considerably the process of healing. Clinical experience has shown by abundant examples the very mediocre healing power of both tendon sutures and tendon grafts within a synovial sheath, especially in the absence of a good mesotenon or when the sheath is entirely surrounded by a dense osteofibrous tunnel. Bier and his pupil Salomon believed

that this was due to the presence in the synovial fluid of a hormone that inhibited tendon regeneration, and that if the sheath were left open so that the tissue juices could in some way neutralize the hormone, healing would take place by true tendon regeneration. This view was strongly contested by Rehn and numerous others. Wehner's experiments in particular are cited in contraversion of Bier's ideas. Wehner excised the patella in dogs and sutured the patellar tendon across the open knee joint where the suture line was constantly bathed in synovial fluid. Despite this, there was perfect regeneration of the tendon.

Hueck studied experimentally in dogs the problem of tendon regeneration within sheaths. He sutured the flexor tendons of the toes in the ball of the foot where they are contained in synovial sheaths. In some instances, the sheath was carefully closed over the tendon suture, while in others, it was left open or a part was cut away. He found that even when good apposition was obtained at operation, the stumps soon separated, and when examined at varying intervals afterward were found to be covered by a very small cap of tissue. This cap came from the thin external peritenonium. It appeared from the results of Hueck's experiments that it made no difference whether the sheath was open or was carefully closed, the cause for failure was apparently the lack of connective tissue capable of proliferation. A lack of blood vessels to the tendons did not apparently impress Hueck as important, except so far as these would be surrounded by connective tissue that could proliferate and lead to union.

Schwarz' exhaustive experimental study of the healing of tendon wounds and the plastic replacement of tendon defects is classic. His paper deals first with the anatomic process of tendon regeneration, its causes and prerequisites. Schwarz worked with the achilles tendon of the rabbit. In some instances the tendon was divided and not sutured, while in others it was sutured; in some the peritenonium (paratenon in this case) was left intact, while in others all of the paratenon and as much as possible of the subcutaneous tissues were excised. He concluded that the paratenon, when present, proliferated to fill the defect, but that this replacement tissue (Ersatzgewebe) is not as functionally efficient as normal tendon, since it tended to lengthen out. Schwarz found that the peritenonium internum also proliferates, but to less extent than the paratenon and only begins to do so about the sixth day, while the tendon cells are quiescent and take no part whatever in the formation of the replacement tissue. The replacement tendon at first is quite nuclear and very vascular, but it gradually loses nuclei and vessels; its irregularly arranged fibers condense and line up in the direction of pull of the tendon, and the nuclei become flat or oval. No matter, however, how much the replacement tendon may resemble normal tendon microscopically, it never does so macroscopically; its

normal mother-of-pearl sheen never returns. The presence of a suture did not change the fundamental basis of the process of healing. A suture kept the ends together better, but, as a matter of fact, did not entirely prevent their separation. Removal of peritenonium externum and as much as possible of surrounding connective tissue emphasized the importance of these tissues in the process of regeneration, since in this case even when the stumps were sutured the gap was not bridged across, the ends retracted, and the proximal stump nearly always became adherent to the surrounding tissues. Schwarz found that when the nerve supply to the muscle is divided the tendon wound heals, but that the tissue is a loose fibrous scar which does not in any manner resemble the replacement tendon (Ersatzsehne), which forms under the stimulus of function.

Schwarz conducted also a number of experiments with grafts, both of tendon and of other tissues, in the repair of tendon defects. In these experiments, he removed from the defect all tissue capable of proliferation and replaced the excised tendon by another tendon plus its external peritenonium. He found that the regeneration here was due to the external peritenonium, which was seen in active proliferation during the very first days. It establishes vascular connections easily with the surrounding tissues and forms a dense envelope about the grafted tendon. The tendon itself becomes partly necrotic, though the more peripheral parts of it remain viable; however, he believed it played a passive and rather unimportant rôle, even though a few mitoses may be seen. According to Schwarz, some other tissue, such as fascia, which is able to establish vascular connection more easily with the surrounding tissues, would serve better as graft.

Hauck believed that tendons heal by the formation of scar tissue due to proliferation of the peritendinous connective tissues. A good blood supply is necessary for good healing, and Hauck noted that, even in the case of tendons surrounded by a sheath, healing may occur provided a good mesotenon is present. The scar resultant from healing is never replaced by, or transformed into, true tendon. The tendon itself plays no part in the actual repair.

Salomon, a pupil of Bier, studied the process of tendon repair and suture within a sheath. According to him, the poor healing power of tendons enclosed within a sheath are due to two factors. One of these is the synovial fluid which inhibits growth probably through a hormonal action and certainly in that it keeps connective tissue away from the area. The other factor is a paucity of tissue capable of proliferation. Tendon heals essentially by the proliferation of the peritenonium externum and internum. In cases of tendons not enclosed in a sheath, the paratenon furnishes an abundance of tissue capable of proliferating.

In the case of sheath-covered tendons, the synovial layer covering the tendon is very thin and can proliferate poorly, and the peritenonium internum is also scanty. Salomon did find, however, that by performing tenotomy above the sheath and by suturing the tendon within the sheath union would occur. This union, however, was dependent on securing a close suture which held the stumps well together, since otherwise too great a gap would result for the scanty regenerative powers of the tendon to bridge. He suggested in intravaginal suture leaving the sheath open or excising parts of it in order to allow the suture line to come into contact with the subcutaneous tissues.

Imayoshi's experiments with vital staining tend to bear out Borst's and Enderlen's position—that the healing of the defect is due to tendon cell proliferation. This investigator believed he was able by a method of vital staining (Kiyono) to distinguish between tenoblasts and fibroblasts. The tenoblasts come from the stumps, not directly on the line of tendon division, but slightly removed therefrom; they never come from connective tissue cells and never form by metaplasia from other cells. The first tissue to fill up the gap is fibroblastic; this, however, is later replaced by tendon cells.

Migliavacca, from an experimental study of tendon wounds of the tendo achillis in rabbits, found that the tendon cells were actively proliferating by the third day, and that they could be seen penetrating the gap. These cells have abundant protoplasm, large nuclei and lightly colored intermediate substance, and the tissue they form becomes differentiated into new tendon tissue. These new cells or tenoblasts take the principal part in the formation of the tendon callus. By the fifth to the sixth day they begin to assume the appearance of tendon cells with elongated nuclei; by the tenth day fibrils arise in their protoplasm, and by the thirtieth day they have become regularly arranged in long parallel rows.

Max Lange's critically planned experiments have led him to conclude that the regenerative power of the tendon itself is not great. He found that if the external peritenonium and subcutaneous tissues were prevented from entering into the formation of the tendon callus, "tendon regeneration" did not occur. He did not question that tendon cells may regenerate, but he did not lay any stress on this regeneration in the process of tendon healing.

Bloch and Bonnet, in a long report on tendon surgery of the hand before the French Congress of Surgery in 1929, agreed in the main with Schwarz that the tendon callus is a replacement tendon and not a true tendon. The "Ersatzsehne" can always be differentiated from true tendon, and it is a question whether the tendon cells take any but a very minor part in its formation.

EXPERIMENTAL DATA

STATEMENT OF PROBLEM

The repair of tendon defects apparently depends on the proliferation of tissue from several sources. The problem is to determine the interrelationship of the different proliferative processes and their significance as regards the final result of a tendon suture or a tendon graft. Does repair of the defect come about mainly as the result of reparative powers of the connective tissue elements in and about the tendon? Do the proliferative changes noted within the tendon itself contribute toward the final result? Do both of these processes have definite and distinct functions in tendon repair? What is the practical surgical application of a knowledge of this repair?

GENERAL OUTLINE OF EXPERIMENTAL WORK

In the present series of experiments sixty-nine dogs were operated on. In thirty-five of these, a tendon was divided and immediately sutured. In thirty-four a segment of a tendon was excised and immediately replaced by a segment of another tendon from the same dog. Certain of these dogs were allowed free and full use of the extremity immediately following operation. In others, the leg operated on was immobilized in a plaster cast for varying periods of time following operation. At various intervals after surgical repair of the tendon the legs were examined, the operative field exposed, and the tendon removed for microscopic section and study. In a few experiments the presence of a gross infection led to a discard of the material; in a few instances material was lost; in all, however, thirty specimens of suture and twenty-nine of graft were examined microscopically. It is on the results of these microscopic examinations that this report is based.

PROCESS OF TENDON REPAIR AS REVEALED BY EXPERIMENTS WITH TENDON SUTURE

TECHNIC OF EXPERIMENTS

Experiments with tendon suture were performed on thirty-five dogs. In all experiments the tendon corresponding in man to the extensor carpi radialis (which is a double tendon) was divided and immediately sutured. The type of suture, with the exception of dogs S 6 to 16, inclusive, was the usual type of lacing suture used by Kanavel and Koch. In dogs S 6 to 16, an attempt at a splicing suture was made, in that a small segment was cut from the side of each stump, left attached to its mesotenon and placed in the gap as a sort of pedunculated graft. In the first five sutures of this type no tension suture was used; in the second five a tension suture accompanied the usual fine apposition sutures. The treatment accorded the sheath also varied somewhat in the different experiments. In dogs S 1 to 6 and in S 9, the sheath was split longitudinally and closed; in dogs S 21 to 35, it was split longitudinally and not closed; in dogs S 7 and 8 and S 10 to 13, the sheath was slit transversely and sutured, and in S 14 to 20, it was slit transversely and not sutured. Immobilization was not attempted in dogs S 1 to 16, while in S 17 to 35, a plaster cast was placed on the leg to secure maximum relaxation of the tendon.

PROTOCOLS OF EXPERIMENTS WITH TENDON SUTURE

FOUR DAYS.—*Dog S 35.*—The tendon was divided and brought together satisfactorily with a lacing suture, and a cast was applied to keep the leg flexed and the radiocarpal joint extended.

The area of suture was examined on the fourth postoperative day. Healing had occurred per primum. The tendon ends, still united by the suture, had separated 1.5 cm. and were covered by hemorrhagic and edematous tissue. Union appeared to be due mainly to the surrounding tissues, since, although a pull of 11 pounds (5 Kg.) did not break through it, it broke easily with a slight pull after the peritendinous tissues were divided.

Microscopic examination of a cross-section of the proximal stump showed it to be badly disrupted by the suture material about which was seen some tendon degeneration. The tendon itself showed no evidence of proliferation, although the nuclei were possibly slightly larger than normal. The fibrous septums were thicker than normal. Along the borders of the tendon, the sheath was thickened and was fused to the tendon. The gap was filled with granulation tissue. The distal stump showed practically no change in the tendon cells. The fibrous septums, however, were thickened, and there was an increase of cells about the intratendinous vessels.

SEVEN DAYS.—*Dog S 34.*—This was a fairly satisfactory suture. A cast was applied. The wound healed per primum. The stumps had separated approximately 1.5 cm. and the suture had pulled out of the proximal stump. There had been proliferation of the sheath and peritendinous tissues, but none, so far as gross examination could determine, in the stumps.

Longitudinal sections of the distal stump microscopically showed little change in the tendon, except that due to the disruption caused by the silk. However, at one place, the nuclei in the tip were increased in number, and where the tip joined the intervening tissues it fused with them so that definite delimitation was absent. The sheath tissues about the stump were thickened and dipped into the gap to form a strand that extended toward the proximal stump. The gap tissue was made up of the proliferated sheath in which most of the fibers and nuclei were arranged in longitudinal rows parallel to the tendon pull. There was a moderate leukocytic infiltration about the silk suture.

A cross-section through the proximal stump showed few changes, except a thickening of the fibrous septums.

Dog S 24.—On uncovering the operative area, it was found that there had been a separation of about 2 cm. bridged across by fibrous tissue which successfully transmitted the pull. The newly united tendon appeared to glide easily through the surrounding tissues.

A longitudinal section through the whole specimen showed a union of the two stumps effected by the proliferated sheath tissues, which, passing over the stumps, dipped into the gap and formed there a dense strand. In this strand the fibers and nuclei were lined up in rows parallel to the line of pull of the tendon (fig. 1 *D*). The proximal stump showed an increase in number of nuclei in scattered areas throughout, and at the end of the stump the tendon fibers were seen to pass into a triangular zone of tissue which covered the tip and lay between the proliferating sheath tissues which dipped down about the stump to lie in the gap. This triangular zone (fig. 1 *B*) was made up of granulation tissue in which an orientation of fibers was already taking place. The intratendinous vessels were wide and dilated, and there was an increase of cells about them. The septums of the tendon were also thickened and more cellular than normal.

The distal stump also showed some proliferaive changes. There was some increase in the number of nuclei even at some distance from the suture line (fig. 1 *C*), though the changes here were certainly less advanced than in the proximal stump. The sheath about the stump was thick and dipped over the end of the stump into the gap, where it fused with the proliferated sheath tissues from the proximal stump. The small triangular zone at the tip was disorganized and had not been invaded by fibrils from the stump.

Dog S 33.—A nice approximation was obtained, and a cast applied. The dog was killed seven days later. There had been some separation of the stumps, and the gap had been bridged across by fibrous tissue. A pull of 2½ pounds (1.1 Kg.) broke through the union just distal to the tip of the proximal stump.

Microscopic examination of cross-sections of the proximal stump showed considerable disruption of the tendon fibers, evidently due to the trauma of suturing. There was considerable thickening of the fibrous septums and sheath, and in places it was quite difficult to be certain that areas that looked like fibrous tissue were not in fact proliferating tendon. The gap tissue was apparently entirely granulation and fibrous tissue, presumably from sheath and peritendinous tissue proliferation.

Fourteen Days.—*Dog S 7.*—A splicing suture was used without tension suture, and the sheath was closed with plain catgut. No cast was applied. Fourteen days after operation the area was again exposed. The tips of the stumps were covered by dense adhesions which involved the deep fascia of the leg.

Microscopic examination showed that the tendon nuclei in the proximal stump had increased considerably in number. This increase was noted particularly in the tip of the stump, but was also present well up the stump as two broad nuclear strips. The increase in vascularity and fibrous septum proliferation noted in early specimens was seen here also. From some parts of the end of the stump, young tendon fibrils and nuclei could be seen to push distally into the gap. The sheath about the stump was thick and ran continuously from one stump to the other.

The gap between the two stumps was filled by a rather dense fibrous tissue in which were embedded the two segments of tendon tissue used originally to help splice the gap. In general, the tissues were lined up in rows parallel to the line of pull of the tendon, though the closer one approached the distal stump, the less definite this orientation became. Blood vessels were rather plentiful. The two bits of tendon included in this region were both alive and very nuclear and fused with the surrounding tissues. Mitotic figures were plentiful in these bits of tendon.

The distal stump did not end quite so abruptly as it had in earlier specimens. It showed instead considerable increase in the number of nuclei and many mitotic figures, especially at the tip; it passed over imperceptibly into the gap tissues. The fibrous septums were more nuclear and thicker than had been noted before in the distal stump. The sheath tissues had fused with the sheath from the proximal stump.

Dog S 17.—The divided tendon was easily and accurately sutured without an excess of tension. A cast was applied. The area of suture was again exposed two weeks later, and the specimen excised. The area of suture was easily uncovered and was not adherent to the fascia. The stumps had separated 2.2 cm. since suture, and were united by a small fibrous-like cord. The proximal stump was slightly bulbous. The distal stump looked gray and necrotic at the tip. The stumps and gap were covered over by a thin, shiny membrane.

Microscopic examination showed that the gap had been bridged across by the sheath and peritendinous tissues which had fallen into the defect and formed a dense strand from stump to stump. The tendon itself in the proximal stump showed

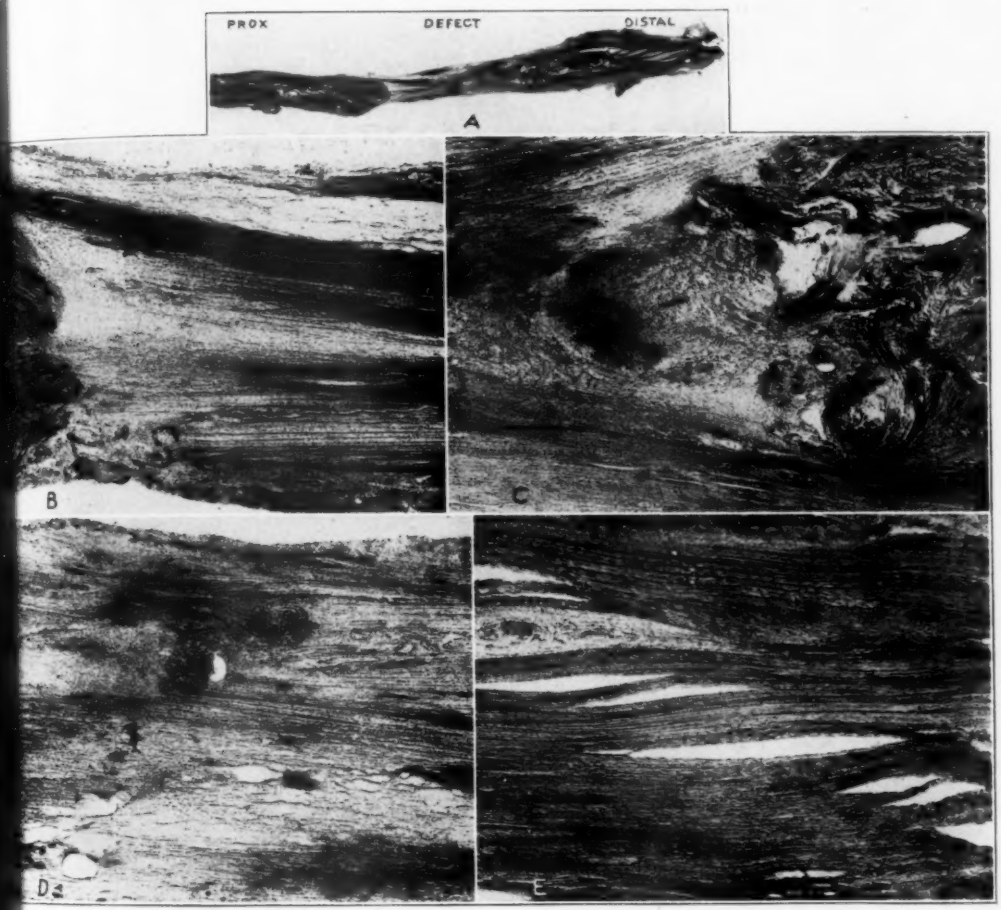


Fig. 1.—Sections through specimen S 24, which show the changes at the end of one week. *A*, entire specimen under very slight magnification. The proximal stump (*Prox.*) is thickened, and its sheath has spread distally over the end into and across the defect to meet the proliferated sheath tissues from the opposite stump (*Distal*). The ends of both stumps are clearly visible. *B*, the end of the proximal stump; × 13. The stump ends very distinctly against the triangular area of tissue contained between the converging layers of the sheath, which are lining up in long parallel rows of fibers. *C*, the tip of the distal stump, is very much disrupted by the silk suture material which certainly interferes with the growth of tendon fibers proximally. *D*, the tissue from the central part of the defect, composed mainly of longitudinally arranged sheath tissues. *E*, a section taken from the distal stump, somewhat back from the end. This shows the straightening out of the fibers and the increased nuclearity of the tendon. A blood vessel with increase in tissues about it is also shown.

evidences of proliferation throughout the whole area of the section. The increase in number of nuclei was so great in places that the collagen fibers were either obscured or had disappeared, and mitotic figures were plentiful. At the end of the stump, the nuclei became much more numerous and the tendon fibers less and less distinct; a general transition occurred between the stump and the intervening tissues.

The gap tissue was made up of proliferated sheath and peritendinous tissues, with the addition of fibers from the proliferating tendon. Toward the middle of the gap, the uniting tissue became very thin, only to widen out again as the distal stump was approached.

The distal stump showed approximately the same picture as the proximal stump, except that it was not so far advanced.

Dog S 6.—In this dog, the tendon was sutured by means of a splicing suture, without the use of tension suture. A cast was not applied.

Examination on the fourteenth postoperative day showed that few adhesions had formed between the suture line and the surrounding tissues. The stumps had separated approximately 3 cm., and were united by rather soft-looking young connective tissue in which were embedded the two bits of tendon that had been excised from the stumps and used to splice the gap. The stumps and gap were covered by a paratenon-like sheath.

Microscopic examination was unsatisfactory, owing to the fact that the specimen had been partially dissected. Both stumps showed marked nuclear proliferation, tendon cell mitoses and partial fusion of their fibers with the gap tissues. The gap was filled by an organizing granulation tissue, by the proliferated sheath and to some extent by fibers coming into it from the tendon ends.

Dog S 14.—A splicing suture and tension suture were used. No cast was applied. The specimen was removed two weeks after operation.

Microscopic examination showed that the stumps were held together by proliferation of the sheath tissues and mesotenon, which formed thick strands passing from one tendon end to the other. The cells and fibers in the uniting tissues had lined up in parallel rows along the course of pull of the tendon. Neither stump showed marked proliferation; there was an increase in the number of nuclei, however, and mitoses were present.

Dog S 15.—The procedure in the experiment was practically the same as that described for S 14.

Microscopic examination showed that the whole specimen was diffusely infiltrated with leukocytes. In the proximal stump, the fibrous septums were thick and nuclear, and many mitoses were seen. The tendon itself was much more nuclear than normally, especially toward the tip, where the nuclei were so numerous as to obscure the collagen fibers. Many mitoses were seen scattered throughout. At the end of the stump, the tendon tapered off gradually, still maintaining its increase in nuclei, and fused imperceptibly with the gap tissues. Suture material embedded in the stump was surrounded by inflammatory infiltration with occasional giant cells.

The tissue in the gap was made up in the main of sheath proliferation. The most proximal bit of splicing tendon was alive and showed about the same proliferative changes as the proximal stump with which it had fused. The nuclei were increased in number, fatter and more vesicular than normal, and numerous mitoses were seen. The gap tissue more distally was made up of granulation tissue, centrally about which was the fibrous sheath.

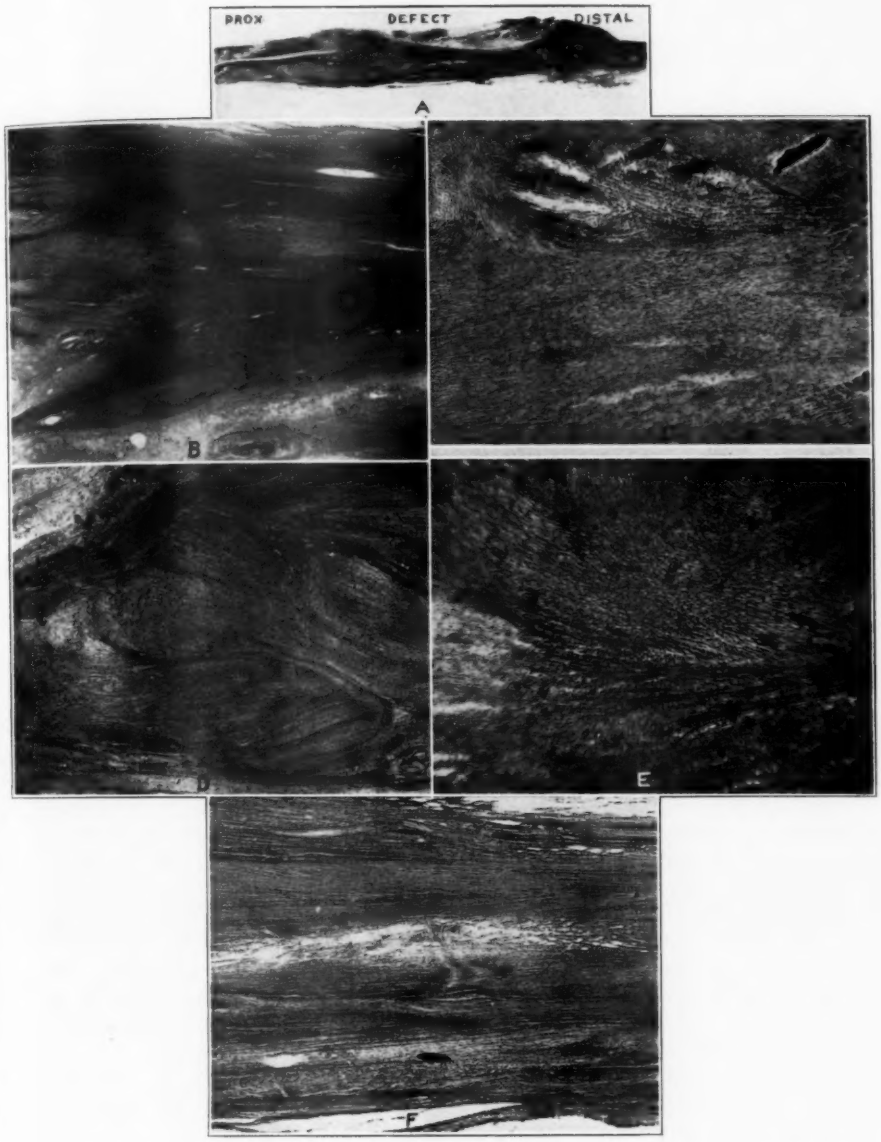


Fig. 2.—Sections through specimen S 22 showing the progress of healing at the end of the second week. *A*, the bulbous tip of the proximate stump *(Prox.)*, has proliferated and sends fibers distally into the gap with which it fuses, without a definite zone or line of boundary between tip and intervening tissues being distinguishable. The distal stump also is beginning to proliferate, and, while more definite and distinct than the proximal stump, is also beginning to fuse with the tissues in the defect. *B*, the tip of the proximal stump. Here the proliferated fibers from the stump are continuous with those of the defect, and, as shown in *C*, no delimitation is possible. *C*, the end of the proximal stump at the place where it passes over into the gap. *D*, the end of the distal stump. Despite disruption by the silk, the tendon is proliferating, there is great increase in number of nuclei, and the tendon is spreading out fanlike into the intervening tissue at its tip. *E*, the end of the distal stump, showing the fanlike spread of the proliferating tendon; reduced from a magnification of × 45. *F*, section, reduced from a magnification of × 12, of tissues from the central part of the defect. This shows the sheath tissues forming a strong, well oriented, fibrous union.

The distal stump also showed evidences of tendon cell proliferation, especially about the periphery, where it had fused with the gap tissues. There was slight inflammatory infiltration about the silk suture. The sheath about the stump was thick and vascular and fused with the gap tissues.

Dog S 22.—An end-to-end suture was done under considerable tension in this case. A cast was applied.

Microscopic examination (fig. 2) of the proximal stump showed so much nuclear proliferation that the eosin-staining collagen fibers were obscured. The whole stump had lined up in long rows parallel to the line of pull of the tendon. The fibrous septums within the stump were broad and thick, and the blood vessels in the stump had increased in number. At the tip, the stump tapered off somewhat and became continuous with the tissues in the gap (fig. 2 *B* and *C*). The sheath tissues, especially about one side of the stump, were thick and passed over the end of the stump to help form the intervening tissue.

The intervening tissue or gap tissue was a broad, dense, fibrous band, which apparently came partly from the stump and partly from the sheath (fig. 2 *F*). As the middle of the gap was approached, the gap tissue became narrower, only to broaden out again when it neared the distal stump. Here it was again continuous, on the one hand with the end of the tendon, and on the other with the proliferated sheath of the distal stump.

The distal stump (fig. 2 *D* and *E*) was also proliferating, and was literally packed with nuclei. It fused imperceptibly with the intervening tissues with which the sheath also fused.

Fifteen Days.—*Dog S 21.*—An end-to-end suture was done with good apposition and without a great deal of tension. A cast was applied. Examination on the fifteenth day showed a separation of 2 cm. bridged across by fibrous-like tissue which transmitted the pull of the muscle. There was very slight adherence to the skin and fascia about the tendon.

Microscopic examination showed that the proximal stump was very nuclear throughout its whole length, and that its fibers were arranged in long rows parallel to the line of tendon pull. Toward its distal end, the stump began to taper off and to become continuous with the gap tissues. The silk had caused considerable commotion in the stump, and there was still a great deal of inflammatory reaction, and foreign body giant cells were not rare. The blood vessels were more plentiful than in normal tendon, and there was increase in the tissues about them. The normal fine connective tissue septums of the tendon were also wide and cellular. The sheath about the stump was thickened and dense, with its nuclei and fibers flattening out and lining up along the line of pull. These proliferated tissues passed distally over the end of the stump to fuse with the rest of the gap tissues, forming a tough fibrous strand.

The intervening tissues uniting the stump were made up of cells and fibers from the sheath, from peritendinous tissues and from the stumps. Toward the distal stump a silk suture and its knot had made a defect in the replacement tendon, and there was here a small area of inflammatory infiltration. The gap tissues, however, were securely fused to the stumps at each end.

The distal stump showed practically the same appearance as the proximal, i. e., proliferation of nuclei and fusion with the gap tissues.

Dog S 32.—The tendon was united nicely without undue tension, and a cast was applied to maintain relaxation.

The area was examined fifteen days later. The fascia and skin separated easily with a minimum of adherence. The tendon stumps had separated about 2 cm., but

were held together by a thick, fibrous strand, in which the silk suture was embedded. The whole region was covered by a glistening membrane, under which or through which the tendon moved. A pull of 28 pounds (12.7 Kg.) on the freed tendon broke the union at the tip of the proximal stump.

Microscopic examination was made of the distal stump only, which was seen to be very nuclear. Where the nuclei were thickest, the fibers were fewest. The fibrous septums in the tendon were wide and cellular. The sheath, while quite thick, did not appear to be very adherent to the tendon.

EIGHTEEN DAYS.—*Dog S 5.*—Both legs were operated on, and a tendon suture performed on both sides. No casts were used. Examination of the sites of suture was made eighteen days later.

On examination, it was seen that both stumps had separated about 4 cm., and that they were united by very thin strips, and the suture material was seen surrounded by red inflammatory tissue.

Microscopic examination showed about the same histologic picture in each stump. The proximal tendon end was bulbous, being covered by a thickened sheath which extended for a short distance beyond the stump before it broke up into loose strips of tissue. The fibrous septums were thickened and nuclear, the intratendinous vessels were increased in number, and there was perivascular infiltration or proliferation about them. At the end of the stump, the tendon had proliferated into the gap tissues, which were then made up of tissues from the sheath, the intratendinous connective tissue and the tendon proliferation. The distal stump had the same make-up as the proximal stump.

Dog S 11.—In this experiment a splicing suture with tension suture was performed. No cast was applied. Examination was made on the eighteenth postoperative day, and showed that there were few adhesions about the line of union which had separated about 2 cm. The area of suture was covered by a sheathlike membrane, firmly adherent to the region of suture, which did not permit gliding.

Microscopic examination showed that the gap was bridged across by a narrow strand of dense parallel tissue which appeared to have come from the mesotenon. The stumps, while very nuclear, had not produced enough tissue to bridge the gap, but had fused with the strand of dense tissue that united them.

Dog S 20.—A good approximation was obtained after division of the tendon and separation of it from its mesotenon for a distance of about 1.5 cm. on each stump. A plaster cast was applied.

Examination eighteen days later showed that the skin and fascia separated easily from the area of operation. However, the bulbous stumps and the thickened mass of tissue in the gap were firmly adherent to the underlying bone, allowing no motion whatever.

Microscopic examination showed that the ends of the stumps and sheath tissues projecting into the gap had become necrotic, owing probably to the fact that the mesotenon had been removed and that suture material under considerable tension had disrupted the tendon. The proximal end of the proximal stump was still viable and showed increase in number of nuclei as well as thickening of the fibrous septums. More distally, however, the tendon became quite thick; the tendon bundles, owing to cellular proliferation, became quite wide and spread out fanlike into the bulbous part of the tendon and then ended in a necrotic, inflammatory mass. The sheath tissues over the stump had proliferated somewhat and projected beyond the end of the stump, only to become involved in the necrotic, inflammatory mass that filled the gap.

The gap was filled with a thoroughly unoriented mass of granulation tissue.

The distal stump showed practically the same histologic picture as the proximal stump.

TWENTY DAYS.—*Dog S 19.*—An unsatisfactory end-to-end suture was made after separation of the proximal stump for 0.75 cm. from its mesotenon. Even with a great deal of tension, approximation to 0.75 cm. only was obtained. Examination twenty days after operation showed the skin and fascia freely separable from the line of suture. Adherence was present to other surrounding structures, however, since pull on the muscle failed to be transmitted.

Microscopic examination of the proximal stump showed a slight nuclear increase in its proximal end, with some thickening of the fibrous septums. The place through which the suture passed was quite bulbous, and about the silk was considerable infiltration with white blood cells and occasional giant cells. Distal to this bulbous area, the tendon narrowed down somewhat, and the nuclei were increased in number, though not to the extent they were in earlier specimens. Where suture material (knot) lay against the end of the tendon, the tendon fibers stopped abruptly; in other places the tendon passed imperceptibly into the gap tissues. The sheath and peritendinous tissues were thickened and had become oriented along the line of pull.

The gap had been securely bridged across along one side, mainly by the sheath and the peritendon tissue.

The distal stump was more nuclear than the proximal stump, and many mitoses were to be seen, especially in the region in which the stump passed imperceptibly into the gap tissues. The sheath tissues over the distal stump were also thickened and on one side were continuous with similar tissues from the proximal stump. Here they were dense, the nuclei being flattened and lined up in long rows along the line of tendon pull.

TWENTY-ONE DAYS.—*Dog S 3.*—A rather unsatisfactory suture with poor approximation was obtained on each leg. No cast was applied.

Examination three weeks after operation showed a separation of the stumps of 2 cm. on the right and 3 cm. on the left foreleg. The distal stump on the right side looked soft and necrotic, and a pull on the muscle above it was not transmitted. On the left side, however, some of the pull was transmitted, indicating that some function had been restored.

Microscopic examination (fig. 3) showed that there had not been the amount of separation of the stumps that the examination of the gross specimen suggested. The proximal stump was very nuclear throughout, though especially so at its tip, where numerous mitoses were seen (fig. 3 *D*). At its tip (fig. 3 *B* and *C*), it was not possible to determine just where the stump ended, since it blended imperceptibly with the gap tissues. The sheath over the proximal stump was thickened, and its nuclei and fibers were arranged in long rows parallel to the tendon pull.

The gap tissue was wide and looked tough and strong; most of it was a direct continuation of the stumps, only a small part apparently coming from the sheath. The whole of the gap was well supplied with blood vessels, most of which ran longitudinally.

The distal stump (fig. 3 *F* and *E*) looked a good deal like the proximal stump, and it, too, fused with the sheath tissues.

The histology of the tendon suture from the left leg was practically the same as that of the right leg.

Dog S 4.—This experiment presented the same histologic picture as the preceding one.

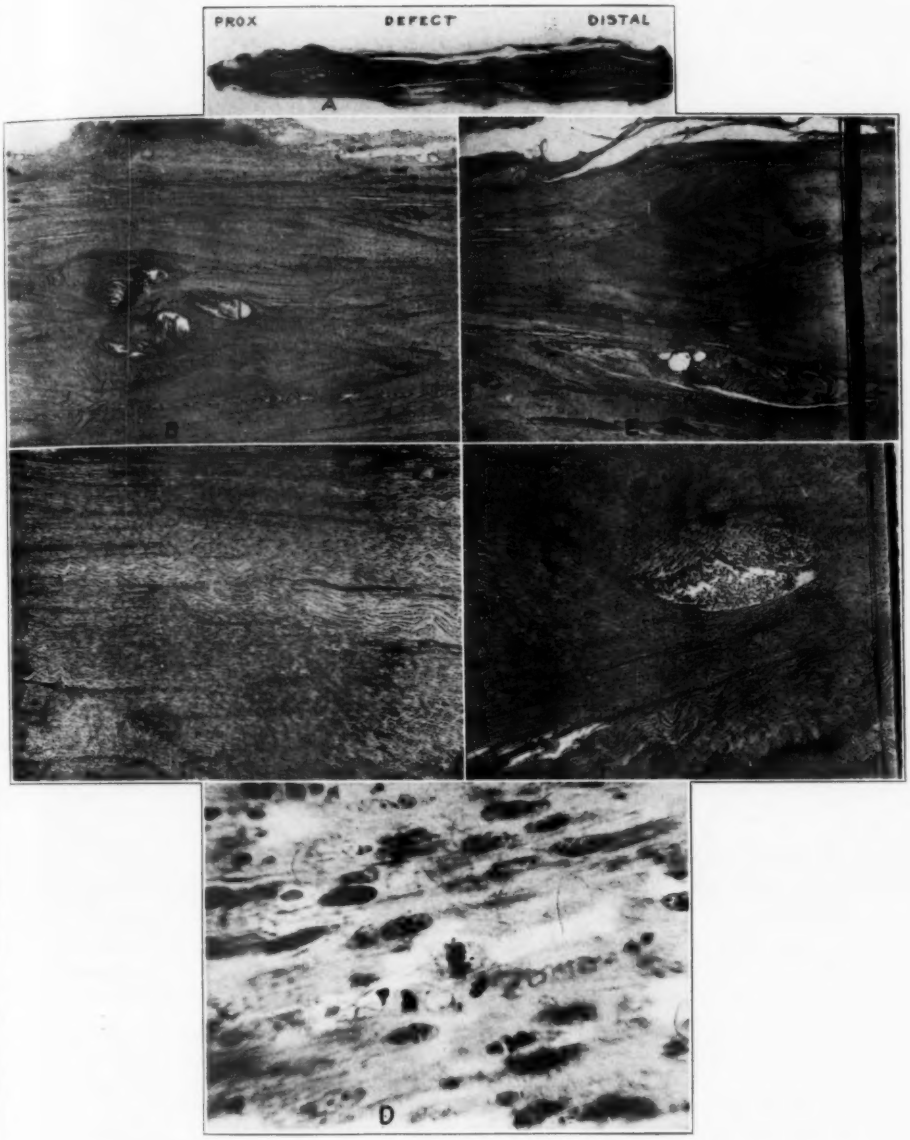


Fig. 3.—Sections through a three weeks old specimen S 3 (right leg). *A*, the entire specimen including proximal (*Prox.*) and distal stumps and intervening tissues. This shows that the proliferation from the two stumps has formed a central band of union between the stumps and that the sheath tissues have become more lax and are loosening up from the regenerating tendon. *B*, the end of the proximal stump, is highly nuclear and still shows evidence of active proliferation. It is continuous with the defect tissues, which cannot be distinguished from the tendon stumps. *E*, the end of the distal stump, is also continuous with the tissue in the gap. *C*, the end of the proximal stump, reduced from a magnification of × 35. This photomicrograph was taken through the region at which it was thought the original stump ended. There is irregular but direct continuity of fibers. *F*, the end of the distal stump. This, as does the proximal stump, passes over directly into the intervening tissues. *D*, mitotic figure from the proximal stump.

TWENTY-TWO DAYS.—*Dog S 27.*—An end-to-end suture with slight tension was made, and a cast applied, which the dog wore for two weeks. After removal of the cast, the dog used the leg as freely as before operation.

Examination on the twenty-second postoperative day showed the tendon ends slightly bulbous, though they were well united and transmitted pull through the intervening tissues. The tendon broke through the middle of the bulbous portion of the proximal stump after a pull of 40 pounds (18.1 Kg.) was put on it.

Microscopic examination of cross-sections of the proximal stump showed increase in tendon nuclei and thickening of the fibrous septums. The gap was made up of a wide, thick strand of connective tissue well supplied with blood vessels.

TWENTY-FOUR DAYS.—*Dog S 10.*—A splicing suture was made in fairly satisfactory manner, except for the fact that one splicing segment was nearly torn loose from its mesotenon. No cast was applied.

The operative area was examined twenty-four days later. The skin and superficial fascia were not adherent to the region of suture; however, the tendon was apparently quite adherent to the sheath and the sheath securely attached to the bone, so that no motion was transmitted. The stumps had separated 3.4 cm., and were united by a thin, fibrous strand.

Microscopic examination showed the proximal stumps to be very nuclear, especially toward the tip, where no eosin-stained collagen fibers could be seen. This end went over gradually into the intervening tissues without any break. The sheath over the stump was quite thickened, well attached to the stump and had taken a longitudinally arranged structure parallel to the line of pull of the tendon. It passed over the end of the stump into the gap and took part in the formation of the intervening tissues. If, however, one traced the sheath farther distally, one found that it lost its dense fibrous structure and ended as loose disorganized connective tissue. The mesotenon under the proximal stump was very thick and vascular, and it too continued into the gap for a certain distance as a dense structure capable of withstanding tendon pull. The more proximal of the splicing bits of tendon was still alive and showed proliferative changes similar to those seen in the stump. It blended proximally and distally with the intervening tissues.

The distal stump had practically the same histologic appearance as the proximal. It would appear, then, that the gap between the two stumps had been so great that it could not be bridged without a graft.

Dog S 13.—A fairly satisfactory splicing suture was performed. Examination twenty-four days later showed few adhesions between the site of suture and the surrounding tissues. A sheathlike structure covered the newly formed tissue uniting the stumps, and the new tendon glided freely within it.

Microscopic examination showed that the splicing segments had remained alive and had bridged a gap of 1.5 cm. from stump to stump. The many mitoses and great nuclear increase in each stump were evidence that considerable tendon proliferation had taken place. The sheath was not so dense and fibrous as in previous sections, and was apparently taking over its gliding function.

TWENTY-SIX DAYS.—*Dog S 26.*—A satisfactory end-to-end suture was obtained, and a cast was applied. On examination, three and one-half weeks later, a nicely gliding tendon was found covered over by sheets of fascia. Test of strength was made of this tendon, which ruptured through the proximal stump with a pull of 16 pounds (7.3 Kg.).

Microscopic examination of the material showed that the whole of the stumps and intervening tissues were forming into a unified whole. The stumps were packed with nuclei, and the tendon fibers were not visible toward the tip, where

they went over imperceptibly into the gap tissues. The sheath, while thick, was not so thick as in earlier specimens. The suture material was still surrounded by inflammatory infiltration, but this was not so marked as it had been earlier. The gap tissue was being divided into longitudinal rows of nuclei and fibers and resembled tendon.

TWENTY-EIGHT DAYS.—*Dog S 25.*—A fairly satisfactory end-to-end suture was obtained, and a cast applied. The specimen was examined twenty-eight days after operation.

On gross examination, it was seen that the tendon glided freely beneath a rather thick, sheathlike tissue covering it. This sheath could be opened fairly easily, except for a few loose adhesions which bound it to the tendon. In an attempt to rupture the new tendon, a pull of 40 pounds (18.1 Kg.) was placed on it, which tore the muscle from the musculotendinous junction, but did not stretch or tear the tendon.

Microscopic examination showed that there was a separation of 1.5 cm. The proximal stump was more nuclear than normal tendon, and showed one particularly bulbous area a short distance proximal to its tip into which the tendon bundles passed, spread out fanlike and became exceedingly nuclear. Distal to this bulbous enlargement, the width of the tendon gradually decreased, until it blended or became continuous with the gap tissues. The nuclei in the stump were somewhat longer and more oval than in normal tendon and were lined up in longitudinal rows parallel to the line of pull of the tendon. The fibrous septums in the most proximal part of the stump were thickened. There was some increased vascularity of this stump.

The tissue intervening between the stumps looked like very nuclear tendon tissue. It was lined up in longitudinal bundles, was quite nuclear and moderately vascular and was continuous at either end with the stumps.

The distal stump, which was continuous with the intervening tissues, had practically the same histologic character as the proximal stump.

THIRTY-FOUR DAYS.—*Dog S 29.*—A fairly satisfactory end-to-end suture was obtained, and a cast applied. When examined thirty-four days later, the region of operation was seen to be moderately free from adhesions. The tendon was covered by sheathlike tissue, beneath which it glided freely. After the tendon was freed from all surrounding tissues, a pull of 36 pounds (16.3 Kg.) was insufficient to break through the line of union. Rupture did occur, however, at the musculotendinous junction.

Microscopically, there appeared to be an attempt at reformation of a synovial sheath. The stumps, while still exceedingly nuclear, were beginning to show a more definite alinement of the nuclei and fibers. They were directly continuous with the gap tissues, which were arranged in fibrous bundles as in normal tendon.

THIRTY-SIX DAYS.—*Dog S 30.*—A good end-to-end suture was obtained, and a cast applied. On examination five weeks later, a good functioning tendon was found which glided easily beneath a sheathlike structure. Both stumps were somewhat enlarged and bulbous; the proximal more so than the distal. When tested for strength, after removal of all associated tissues, the new tendon in the gap ruptured at 44 pounds (20 Kg.) of pull.

Microscopic examination was not satisfactory, owing to the disrupturing effect of the test of strength. However, there was some suggestion that the synovial sheath was beginning to reform.

FORTY-ONE DAYS.—*Dog S 16.*—A fairly satisfactory splicing suture was obtained, and a cast applied. On examination forty-one days later, the two stumps were covered by a soft inflammatory mass of tissue, and there was no apparent union.

Microscopically, despite the gross appearance and evidence of considerable infection, the tendons had partially survived, and a union of a sort had been obtained through the soft inflammatory tissue. This union was a thin but dense fibrous strand in which the fibers and nuclei were lined up in parallel rows along the line of pull. The stumps, which were quite nuclear, passed over imperceptibly into this gap tissue.

THE PROCESS OF REPAIR IN A SUTURED TENDON

The examination of the gross as well as of the microscopic specimens of tendon sutures shows that there may be considerable variation between specimens. The variation is not only chronologic, but quantitative and qualitative as well, in that the rate of healing in some dogs may be quite rapid, while in others it may be slow; in some the amount of sheath proliferation may be excessive and so far overshadow the actual tendon cell proliferation that the latter appears unimportant. In some instances, the amount of inflammatory reaction may be so great as to make the suture a failure, or nearly so, while in others, the disposition of the silk within the tendon and the presence of knots between the ends of the tendon seriously interfere with healing. However, the process of healing appears to depend on the regenerative and proliferative powers of the two tissues entering into the formation of tendon. From this study it seems logical to assume that these two tissues (connective tissues and tendon tissue itself) have each a definite rôle or function to perform in the healing process.

During the first few days following suture, examination reveals a considerable amount of swelling and edema in the peritendinous tissues. The tendon stumps are swollen, have lost their natural mother-of-pearl sheen and appear pink or red instead of white. This coloration is due to the hyperemia within the tendon, as is evidenced by the fine longitudinal red striation, which can be seen if the tendon is magnified slightly. The stumps are practically always separated from 2 to 2.5 cm. (rarely more), depending on the type of suture and the adequacy of the immobilization. The suture may still be holding at this time, though it is rarely secure after the third day.

The defect between the stumps is filled by a red gelatinous exudate which can be easily scraped out, and which looks like granulation tissue. It has no tensile strength, does not hold the stumps together, and any function at this time must be due to the suture holding the stumps.

The sheath, which partakes in the general edema, is also thick and edematous, but in this early stage is either not adherent or very slightly adherent to the stumps and can be easily separated from the exudate.

Microscopic examination at the early stage of healing bears out the assumption that proliferative changes, while present in all the tissues, are not advanced far enough to afford functional union.

The stumps, always separated as just noted, end fairly abruptly against an early granulation tissue which lies in the defect. The tendon nuclei are swollen and fat and more round or oval than in normal resting tendon and appear slightly more numerous. Mitoses rarely appear before the fourth day. The intratendinous vessels are wide, and there is an increase in the cells about them. The fibrous septums of the tendon are thicker than normal, and at the ends of the tendon send cellular strands out into the granulation tissue over the tip. The silk suture is surrounded by white blood cells with an occasional giant cell. The distal stump shows the same changes as the proximal, though all through the experiments it has been noted that the proximal stump is always the more advanced.

The sheath tissues about the tendon are thickened and cellular. They have fallen into the gap over the end of the tendon and are taking part in the formation of the intervening tissues. Already, however, the tendon is quite vascular, and its fibers are arranged longitudinally with the line of pull of the tendon.

The defect between the two stumps is filled with an early granulation tissue. There are many red blood cells and fibrin, fibroblasts and leukocytes and beginnings of capillaries. As yet, the tissue is thoroughly disorganized.

About the end of the first week, a fairly definite structural continuity has been established by means of the sheath and peritendinous tissues. On gross examination, there is still seen a good deal of edema and redness, but this has not the same soft gelatinous consistency that was observed in the first few days. The defect between the stumps is now filled by a fusion of the sheath and peritendinous tissues with the organizing exudate to which the stumps are fused. The sheaths have also fused with the stumps, so that pull on the muscle above leads to movement of the whole mass of tissue. The stumps cannot now be separated without tearing up many adhesions. The suture material is usually deeply buried, though at times it is seen lying on the surface of the tendons.

Microscopic examination at this time (fig. 1) reveals a union of the stumps by a tissue proliferation from the sheath and peritendinous tissues. The stumps themselves, however, are beginning to proliferate and take part in the healing.

Both stumps are bulbous and are thicker than normal. This enlargement is due not alone to the presence of suture material, but to actual proliferative changes in the tendon itself. There is a great increase in the number of tendon nuclei. This increase, while especially

marked near the tip of the stumps, is also present (fig. 1 *E*) in strips and zones at some distance from the suture line. In these regions, tendon cell mitoses may be seen. The tips of the stumps are beginning to send out tiny strands of fibers and nuclei into the intervening tissues. The suture material within the stumps is surrounded by a zone of inflammation. In places (fig. 1 *C*) where the suture lies in the tip of the tendon, it causes considerable twisting and injury to the fibers, and the intervening tissue beyond this is less readily penetrated by proliferating tendon.

At this time the tendon appears very vascular, whether this is due only to dilatation of vessels normally present in tendon, or whether there is an increase in the number of tendon vessels, we cannot say. The fibrous septums throughout both stumps are thicker than normal.

The sheath and peritendinous tissues about either stump are quite thick and dip down into the gap at either end and fuse in the center to form a solid band of tissues. The nuclei and fibers in this band are lining up in long parallel rows (fig. 1). Where the sheath dips in over the end of the tendon there is formed a triangular space, having as its base the end of the tendon, and as its sides the proliferating sheath. This triangular space is at first filled with granulation tissue, but at the beginning of the first week it is being invaded by fibers from the proliferating tendon.

The union at this time (the end of the first week) is therefore a sheath union. It is moderately strong and will allow cautious use. The tendon, however, is beginning to proliferate under the protective sheath union.

About the end of the second week the tissues at the site of suture are definitely less inflammatory than before. The redness noted previously is replaced by a healthy pink. The adhesions between the tendons and the superficial fascia are quite loose and may be broken up easily by blunt dissection. The tendon stumps are bulbous, possibly more so than in earlier specimens, and they are fused to a rather fibrous-appearing tissue which bridges across the interval left by the separation. The sheath is still fused to the stumps and intervening tissue, but the outer layers are less dense and allow some movement of the new tendon.

Microscopic study of the tendon at this time shows definite advancement over the condition during the first week (fig. 2). This advancement affects especially the tendon stumps, the participation of which in the bridging of the gap is considerably increased. They show a marked increase in nuclei, not only at the ends, but throughout the stump, so much so in places that the eosin-staining collagen disappears. Where the stumps abut the intervening tissues, they send out long strands of fibers which pass proximally from the distal stump and distally from

the proximal stump. It is not possible at this stage to determine where the stumps originally ended. Mitoses are plentifully found in all parts of the stump.

The suture material within the stumps is still the site of some inflammation, but this is not so marked as it was earlier.

The sheath tissues are still adherent to the stumps and dip down into the defect and assist in bridging it. They are now quite dense and are made up of longitudinal rows of closely packed fibers. The outer layers of the sheath appear to be loosening up.

The triangular areas noted at either end of the stumps in the earlier section have now been organized by the proliferating tendon into an orderly arranged tissue. The parallel longitudinal arrangement of these fibers can be traced clear across the defect (fig. 2 *F*) from one stump to the other.

After the third week, the union is substantially that due to the tendon itself. When a suture is uncovered after the third week, very few adhesions are found between the superficial fascia and the tendon. Most of the swelling has subsided, and the tissues are regaining their normal appearance. Over the suture line, there is seen a thin paratenon-like sheet of tissue which can be easily removed from the tendon and beneath which the tendon can glide easily.

The defect is now bridged across by a rounded strand of tough fibrous-appearing tissue, somewhat smaller than normal tendon. It will withstand many pounds of pull before rupturing, and even at the third week may be stronger than the normal musculotendinous junction. The stumps have not regained their mother-of-pearl sheen, and the new strand of tissue uniting the stumps does not have this sheen.

Microscopic examination (fig. 3) shows the stumps to be less bulbous than before. Gross examination of a longitudinal section shows a continuous tendon-like structure, slightly narrower centrally, surrounded by lax sheets of connective tissue (fig. 3 *A*). The stumps are still very nuclear and mitoses are not infrequent, but the marked proliferation noted during the second week is not present. It is not possible to determine the point where the stumps end; instead there is a continuity of similar tissue stretching from stump to stump. This tissue is definitely oriented in line with the pull of the tendon, and there is some suggestion that it is beginning to form into bundles, as in adult tendon. Numerous longitudinal blood vessels are present in this newly formed tendon tissue.

The sheath tissues are still thick, but are beginning to separate from the tendon, though still adherent by many fine strands. In places there is a suggestion of a new synovial layer, but we have never been able to determine definitely that a new synovial layer actually forms.

PROCESS OF TENDON REPAIR AS REVEALED BY EXPERIMENTS WITH TENDON GRAFTS

TECHNIC OF EXPERIMENTS

To avoid the repetition of details of operative technic, which we do not desire to stress in this connection, a short résumé of the various types of operative procedure of grafts will be given here, and then only briefly referred to in the actual protocols of the experiments that follow.

In all experiments a segment was excised from the multiple tendon of the extensor carpi radialis. The gap thus left, which was practically always greater by 1 cm. than the length of tendon excised, owing to tonic retraction of the proximal stump, was replaced by a tendon graft taken from the same dog. In many instances this graft was taken from the corresponding tendon on the opposite leg; in other instances the original tendon tissue removed was put back into place to serve as a graft after it had been completely severed from its blood supply, while in still others a section of the extensor pollicis longus was excised and used as graft. In most instances, the graft was cut as long as the segment removed originally from the extensor carpi radialis. In a few cases, the graft was longer than the segment removed, but never as long as the resultant defect; i. e., in every instance the graft was sutured under tension. In a few of the earlier experiments, a careful closure of the divided sheath was made after the graft had been sutured in place; in the later experiments, however, sheath suture was not performed.

The suture material used was grade D twisted silk, lubricated with sterile petrolatum jelly. In the instances in which the sheath was closed after the graft was put into place 00000 china silk or 000 catgut was used to suture the sheath.

In dogs T 1 to 13, inclusive, the following method of suturing the graft in place was used. The stretch of tendon was excised, and a graft taken from the opposite leg. Through the center of this graft a strand of silk was run on a long number 11 beader's needle. This suture was then secured to the one stump by a lacing suture (Kanavel tendon suture), the silk again passed through the graft and secured in like manner to the opposite stump. One knot only was used. It was usually, though not in every case, possible to secure good apposition at the time of operation. In dogs T 14, 15 and 16 the gap was bridged across by overlapping the graft on the stumps. The graft was cut longer than necessary to fill the defect, and was laid across the ends of the stumps under tension, and the tendons sutured side-to-side at each end of the defect by through-and-through sutures.

In dogs T 17 and 18 and T 27 to 34, the ends of the stumps and graft were brought together by separate lacing sutures, i. e., the suture was passed back and forth in the tendon after the manner of the Kanavel suture, taking care not to leave any silk exposed. The knots were tied so as to lie between the ends of the tendon. In this manner, no silk lay in the central part of the graft.

In dogs T 19 to 26, the technic was the same as in T 1 to 13, except that the silk, instead of passing straight through the center of the graft tendon, was basted through the graft from end-to-end.

The sheath tissues were carefully sutured over the area operated on in dogs T 1 to 11, while in all remaining dogs no attempt was made to close the sheath. In all experiments, however, the sheath tissues around the graft were carefully preserved. In making the defect in the first eleven experiments, the sheath tissues about the excised tendon were also removed. In the rest of the experiments, however, the sheath was merely split longitudinally and the tendon alone excised. It

was found that in the instances in which the sheath was removed from the defect and in which the periosteum was exposed, very dense adhesions formed which held the graft securely to the bone.

Dogs T 1 to 16 were allowed free full use of the leg immediately after the operation. In dogs T 17 to 34, however, a plaster cast was applied for varying intervals to keep the radiocarpal joint in extension and the humero-ulnar joint in flexion.

PROTOCOLS OF EXPERIMENTS WITH TENDON GRAFTS

FOUR DAYS.—*Dog T 34.*—Transplantation of a 7 cm. piece of tendon plus peritenon was made into a 6 cm. defect of the extensor carpi radiali. A lacing suture was made through each end of graft and through each stump, with good apposition, and a plaster cast was used.

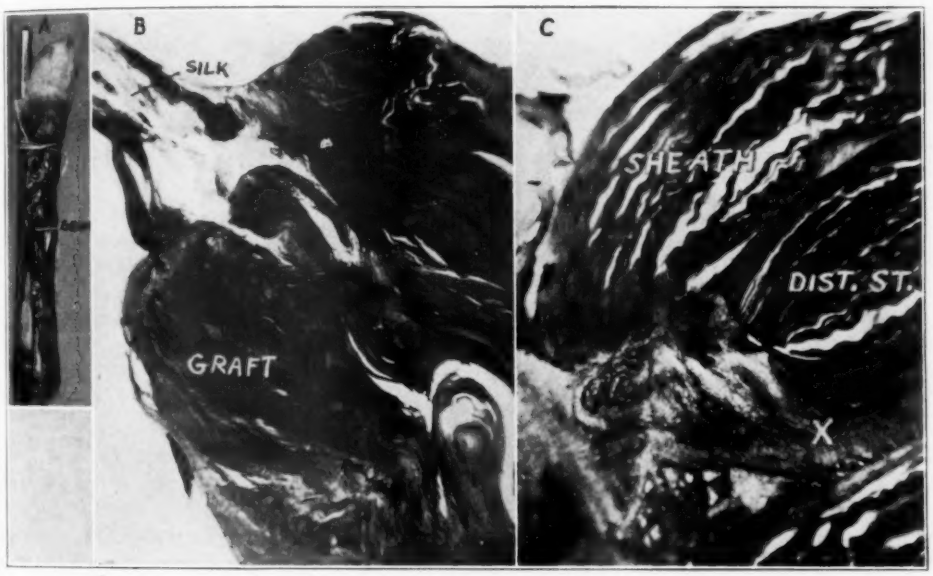


Fig. 4.—*A*, gross specimen of T 34 removed at the end of four days. *B*, photomicrograph of distal end of graft of T 34. *C*, photomicrograph of proximal end of distal stump, T 34; *X* stands for proliferating peritenonium internum.

The dog was killed at the end of four days. The skin and superficial fascia were separated fairly easily from the surface of the graft and stumps. The graft and stumps were swollen and edematous, red and granular in appearance. There was a 7 mm. separation at the distal suture line, still bridged across by the silk, but no separation at the proximal suture line. With traction on the muscle, the tendon pulled through the overlying tissues. A pull of 4½ pounds (2 Kg.) ruptured the tendon through the proximal stump just proximal to the suture line. The graft looked white, but did not rupture with the tension.

Microscopic examination of the distal suture line (fig. 4 *C*) showed that the proximal end of the distal stump was torn and disrupted by the suture, bundles of fibers were twisted about the silk, and there were some evidences of necrosis about these regions of trauma. Except for these areas, the stump was alive. The ten-

don bundles ran straight to the line of suture and then ended quite abruptly, as if cut off. The fibrillar character and wavy course of the tendon were maintained throughout. There were no evidences of nuclear proliferation in the stump. There was an increase in the cells about the intratendinous vessels, which were more prominent than in normal tendon. At the ends of the tendon there were V-shaped spaces between the bundles of fibers. These spaces were continuous with the intratendinous connective tissue (endotenonium) and also continuous with the granulation-like plug that covered over the end of the stump. The sheath about the stump was thickened and moderately infiltrated with leukocytes; it was continuous with the granulation tissue gap over the end of the stump, and was also proliferating over the silk suture that bridged the gap at this place.

The graft was largely viable and had about the same appearance as the distal stump (fig. 4 *B*). The silk here had caused a considerable disruption of the fibers,

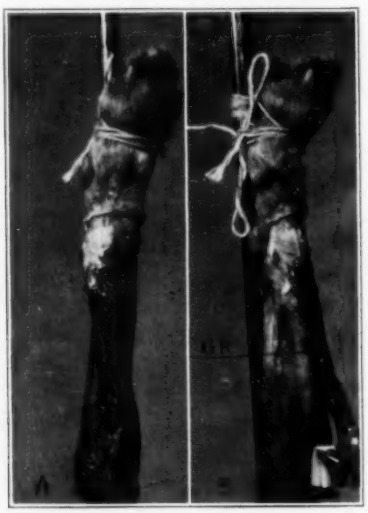


Fig. 5.—Gross specimen of T 32 removed at the end of eight days. *A*, the tendon has not been separated from its bed. *B*, the tendon lifted from its bed. At *Gr.* the graft is shown.

but necrosis was very moderate. The intratendinous vessels were more prominent than normal, and there was an increase in cells about them. Most of the sheath tissues about the graft were alive, were moderately infiltrated with leukocytes and were somewhat thickened. No mitoses were seen in the tendon of the graft which ended rather abruptly alongside the silk suture. There was a thin layer of fibroblastic tissue which was pushing distalward along the sides of the silk suture, and which came apparently from the intratendinous connective tissue.

Microscopic examination was next made of the proximal suture line. It is difficult to determine just why rupture took place through the proximal stump. This stump was long, slim and narrow, but viable; its intratendinous vessels were prominent, and there was increase of cells about them. The area through which rupture took place was frayed and torn, and there was some loss of nuclei here, which might indicate an area of necrosis. In places, the tendon fibers were sepa-

rated by accumulations of red blood cells. The sheath tissues about the proximal stump were very thin, and when traced toward the graft looked as if the parts had been torn away.

Dog T 21.—Lacing sutures were made into each stump, and graft threaded over the silk between the stumps. A cast was applied. The dog died four days after operation. At postmortem examination, no separation was found at the proximal suture line, but about 5 mm. separation at the distal suture line, which was bridged across by the silk. The proximal stump and graft were gray. The whole area of operation showed a moderate amount of bloody exudate.

Cross-sections showed the distal stump surrounded by a rather thick and somewhat edematous sheath from which in several places cellular septums passed into the substance of the tendon. The tendon was not changed much in appearance from normal tendon, although in the areas around the fibrous septums the cell content was increased. This cellular increase was due both to an increased number of cells about the blood vessels and to an increase in the number of tendon cells among which occasional mitoses were seen. The flat type of tendon nucleus predominated, except in the region of the vascular endotenonium, in which the nuclei were becoming fatter and more vesicular. The sheath was somewhat edematous, and showed an area of white cell infiltration and also an area of fibroblastic proliferation.

SEVEN DAYS.—*Dog T 24.*—Transplantation of a 3 cm. graft plus paratenon was made into a defect in the extensor carpi radials. The graft ruffled up when tension was applied. A cast was applied.

The animal was killed at the end of seven days. The skin and superficial fascia were easily separated from the underlying graft and stumps. There was, however, adhesion between the tendon and the deep fascia of the foreleg. There was no separation detectable on macroscopic examination. Pull on the muscle resulted in about 60 degrees of motion at the radiocarpal joint.

On examination of the microscopic specimen with the naked eye (fig. 25), it was possible to distinguish the three areas, the graft and the two stumps. The proximal suture line was very narrow, not over 5 mm., while at the distal suture line there had been some overriding of the tendons, and there was no straight line of apposition. The proximal stump presented a fairly normal appearance (fig. 7 *B*); the tendon fibers were wavy in their course, and there was no suggestion of increase in nuclei until the suture line was approached. There was, however, considerable increase in cells about the vessels lying in the tendon. As the suture line was approached, this perivascular proliferation was seen to push outward into the tissue uniting graft and stump (fig. 6 *A*). At the suture line, the tendon was very nuclear and sent feather-like prolongations into the uniting tissue. In places, the intermixture of tissues was so far advanced that one could not distinguish between the elements derived from tendon, those derived from proliferation of cells about the intratendinous vessels and those coming from the sheath and other tissues that had pushed into the defect. Numerous mitoses were seen in the zone of tendon proliferation (fig. 7 *C*). The silk had produced defects in the stump; these were filled with an organizing granulation tissue that contained a few giant cells.

The sheath about the stump was thick and proliferated (fig. 6 *C*). It was infiltrated with leukocytes, but was beginning to line up in long parallel rows of fibers which ran across the gap tissues to become continuous with sheath tissues of the graft. As the sheath crossed the gap, it sent cellular and fibrous bundles (fig. 6 *A*) into it, which intermingled with the tissue here, while some united with the end of the graft.

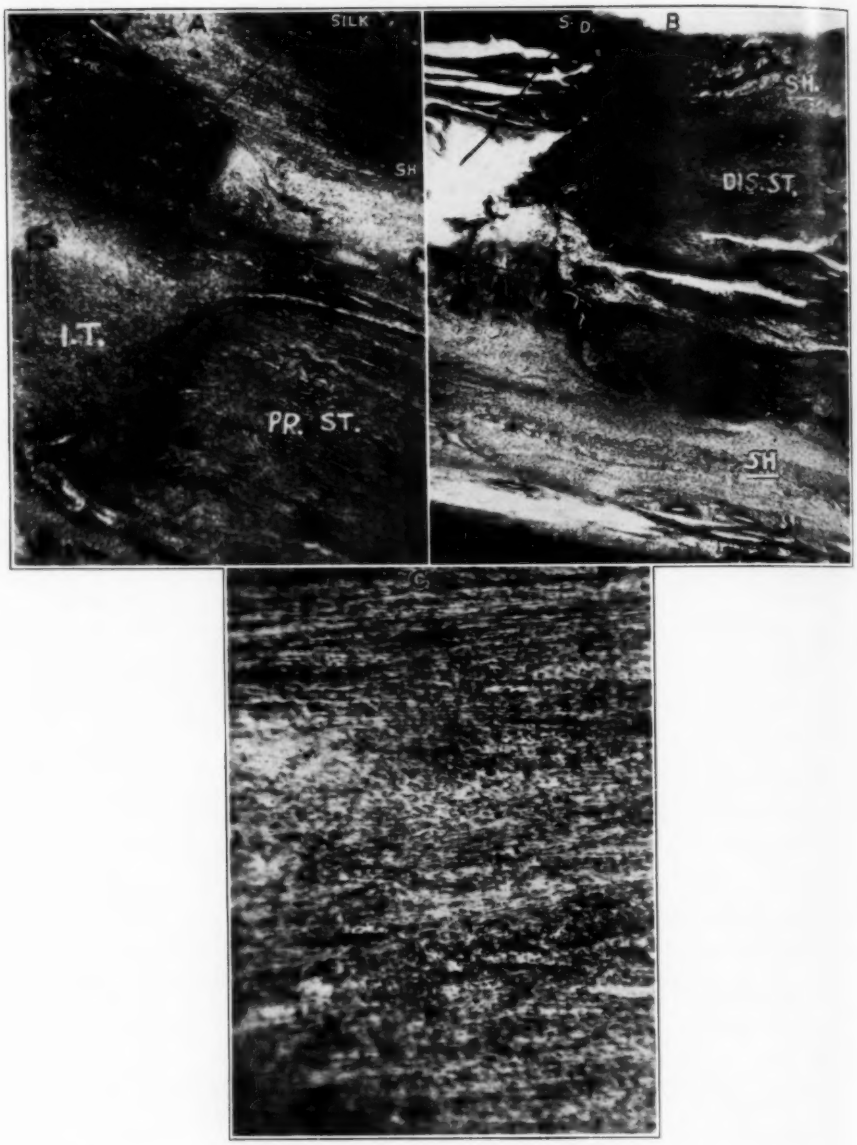


Fig. 6.—Photomicrographs of tissue from T 24 removed seven days after operation. *A*, the distal end of the proximal stump (*Pr. St.*) ends against the intervening tissue (*I. T.*) in a hazy, deeply eosin-stained, irregular edge in which mitoses are seen with higher magnification (fig. 7 *C*, *Mit.*). The sheath (*Sh.*) is thick and proliferated. *B*, the proximal end of the distal stump (*Dis. St.*) surrounded on all sides by the thick proliferated sheath (*Sh.*) ends against a rather large defect, due to the silk suture. *S. D.* stands for silk defect. *C*, the sheath over the stumps and graft is very cellular, but shows definite longitudinal arrangement of its fibers.

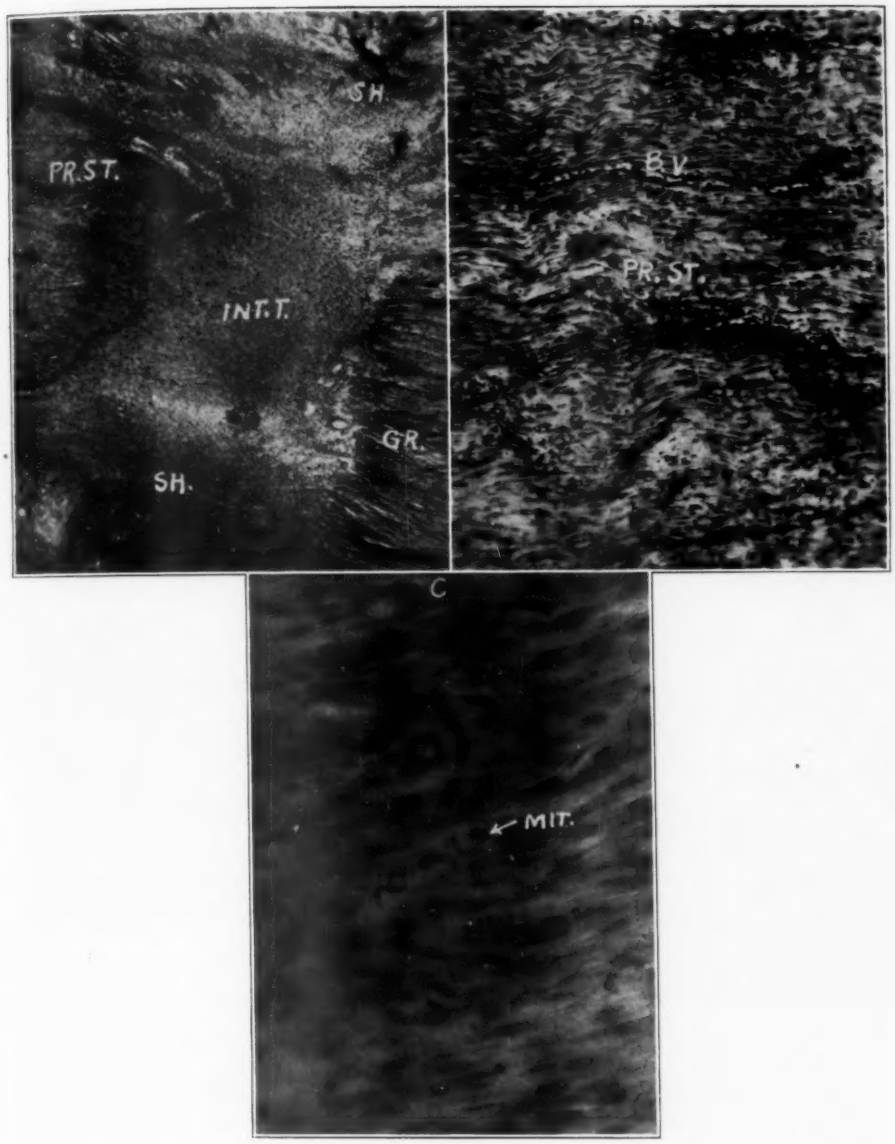


Fig. 7.—Photomicrographs of tissue from T 24 removed seven days after operation. *A*, the proximal suture line shows a small gap between the proximal stump (*Pr. St.*) and the graft (*Gr.*) filled up with a fairly dense intervening tissue (*Int. T.*), while to either side the gap is bridged across by proliferated sheath tissue. *B*, the proximal stump under slightly higher magnification shows the increased number of blood vessels (*B. V.*) and a great increase in number of tendon cells. *C*, higher magnification showing the changes in size and shape of the tendon cells with occasional mitoses (*Mit.*).

The gap tissues (fig. 7 *A*) were beginning to line up in rows parallel to the course of the tendon pull. There were some areas in which giant cells and small round cells appeared to have accumulated around bits of silk.

The graft (fig. 8 *A* and *B*) was readily recognizable as tendon, though it was rather badly broken up by the suture material. At the proximal suture line, it showed a blue cellular zone in which mitoses could be found. It was more vascular than normal at the suture line (fig. 7 *A*), and there was a considerable increase of cells about these parallel vessels. Where the vessels came to an end at the suture line, long rows of fibroblasts and connective tissue cells radiated into the intervening tissues. The nuclear end of the tendon had lost its wavy fibrillar

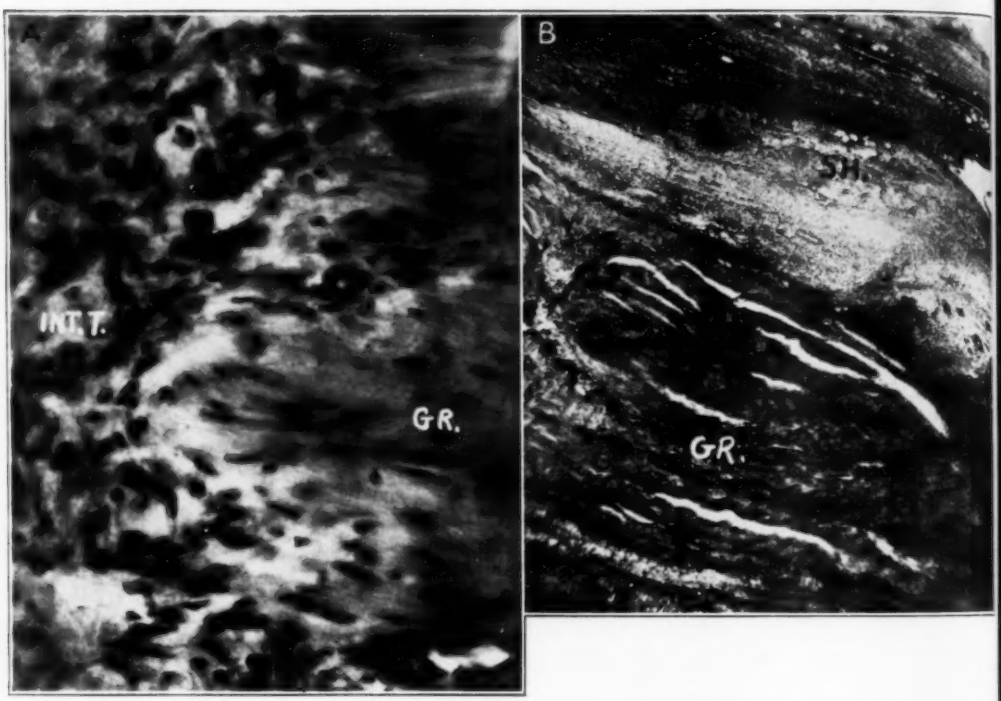


Fig. 8.—Photomicrographs of the graft removed from T 24 seven days after operation. *A*, the proximal end of the graft where it abuts the intervening tissues (*Int. T.*). The changes in size and shape and the increase in the number of the nuclei are well shown. *B*, central part of the graft showing the thick proliferated sheath (*Sh.*) and the nuclear increase in the graft.

appearance; the tissues about the nuclei took the stain more evenly, though one could usually detect a longitudinal arrangement in them. From the end of the graft, feather-like cords of cells pushed outward to become intermixed with the intervening tissues (fig. 8 *A*). Mitoses were to be seen in the end of the graft. The central parts of the graft, especially toward its distal end, showed areas of necrosis, but these were not of great extent. The silk had produced defects which were being healed by organizing granulation tissue. At the distal end, the graft and stump overlapped somewhat. About one half of the distal end of the graft

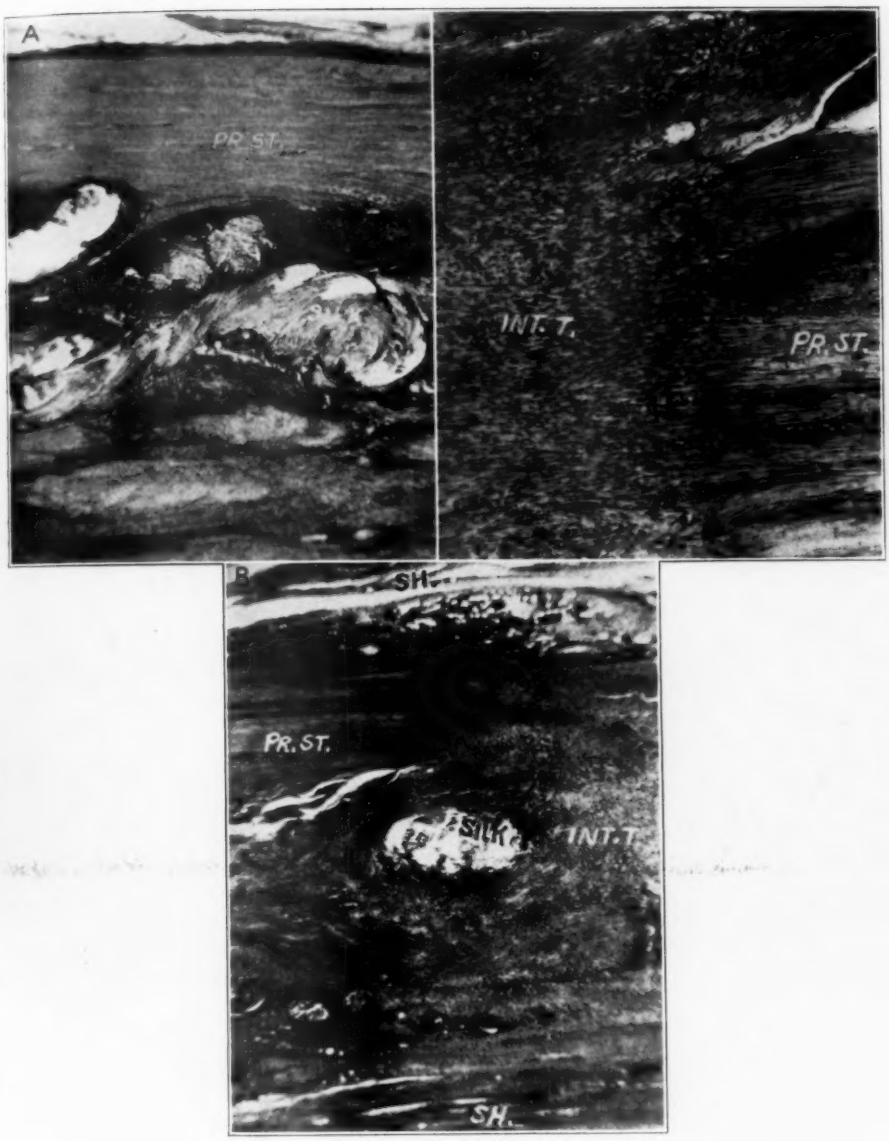


Fig. 9.—Photomicrographs of specimens removed ten days after operation. *A*, the proximal stump of T 5 which shows the destruction caused by the suture material and the increase in tendon nuclei with the straightening of the fibers. *B*, the distal end of the proximal stump (*Pr. St.*) of T 17 ends in a dark blue zone against the intervening tissue (*Int. T.*). The presence of a bit of silk here deflects the proliferating tendon to either side. The sheath (*Sh.*) is seen to be continuous over the defect. *C*, under slightly higher magnification, the hazy end of the proximal stump (*Pr. St.*) of T 17 shows penetration of the proliferating tendon into the intervening tissues (*Int. T.*). The cellular increase about the intratendinous vessels is also well shown.

was necrotic. The other half of the graft was viable and contained many longitudinal blood vessels, but there was not the nuclear increase such as was found in the proximal end of the graft. The sheath about the graft was thick, long strands of connective tissue fibers were forming in it, and it was infiltrated with leukocytes. The sheath was directly continuous with the sheath over the proximal and distal stumps.

The distal stump was badly broken up by the suture about which were leukocytes and occasional giant cells. The tip of the stump showed some increase in cells, but not so much as was seen in the proximal stump.

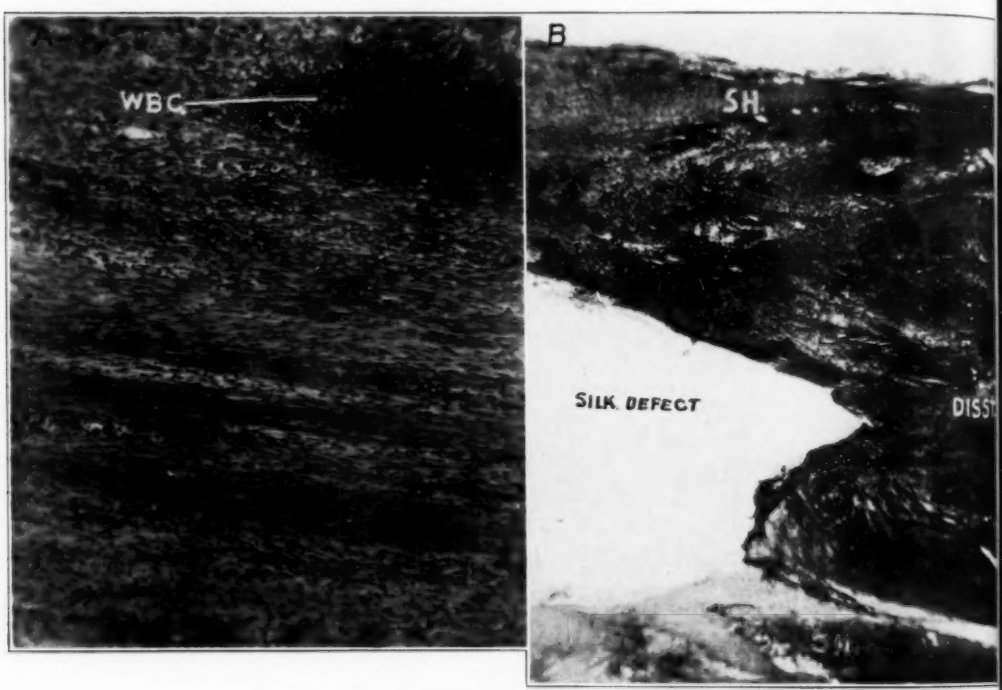


Fig. 10.—Photomicrographs of specimens removed ten days after operation. *A*, the sheath over the distal stump of T 5 is becoming well organized into strong fibrous tissue lined up in horizontal bands parallel to the line of pull. Occasional accumulations of white blood cells are seen. *B*, the distal stump of T 17 (*Dis. St.*) ends abruptly against a defect due to the silk suture. This defect is efficiently bridged across by proliferated sheath (*Sh.*).

Dog T 14.—Transplantation of a 2 cm. graft, taken with its sheath from one extensor carpi radialis, was made into a defect left by removal of 1 cm. from the opposite tendon. The graft was threaded over a double strand of grade D silk and then secured to the stumps by side-to-side suture. The sheath was not sutured, and no cast was applied.

The animal was killed seven days after the operation and the leg examined. There was no union. The graft had entirely disappeared, and the tendon suture

lay in the proximal stump. There were many adhesions about the area in which operation had been performed. The space between the stumps was filled with gelatinous material. The microscopic specimen was lost.

EIGHT DAYS.—*Dog T 15.*—Transplantation of a 2.25 cm. graft plus its sheath was made into a defect left by removal of 1 cm. from the extensor carpi radialis. No cast was applied.

The animal was killed on the eighth postoperative day. The suture lay free between the separated stumps, the gap being filled with a gelatinous material containing small bits of necrotic tendon, evidently the graft.

Longitudinal sections through the proximal stump and the proximal one half of the intervening tissues showed that the gelatinous material referred to was becoming slowly organized (fig. 11 *C*). The peritenonium internum and externum of the proximal stump and the connective tissue in and about the muscle attached to the stump were thickened and contained numerous large blood vessels. On low power microscopic examination, the connective tissues about and in the tendon and muscle were seen to run directly and continuously into the intervening tissues. Also, strands from the end of the stump were pushing distally into the intervening tissue. Some red, eosin-stained areas in the intervening tissues suggested remnants of the graft.

The cellular increase in the stump was quite apparent under higher magnification. The increase was most marked at the end of the stump and became less and less apparent as the proximal part of the stump was approached. From the end of the stump, delicate, feather-like strands of tendon cells could be seen to push distally into the intervening tissues, where they could be distinctly traced for some distance. The nuclei in the tendon at its growing tip were much increased in number and were more oval and not quite so darkly stained as in the enlarged tendon more proximally, and mitoses were to be seen among them.

There was marked increase in the amount of the perivascular tissues within the tendon. The strips of connective tissue, ordinarily narrow and thin, were broad and thick; they were made up of fibroblasts, some few white cells and numerous oval cells with vesicular, well staining nuclei, which were thought to be endothelial cells.

The connective tissues between the muscle and tendon were also thick and proliferated. Although very much infiltrated with white cells, the main substance was made up of long strands of young connective tissue and fibroblasts. These strands along with those from the endotenonium internum pushed distally into the intervening tissues, and with the proliferation from the end of the tendon were serving to establish continuity.

The intervening tissue (fig. 11 *C*) was an organizing granulation tissue which was being invaded by strands from two sources. Proximally, there came strands from the proximal stump and from the connective tissues in and about the stump. From the distal end was another source of connective tissue and tendon, i. e., from the graft and its sheath structures. There were two areas of massive leukocytic infiltration which were being slowly organized. About these areas, however, and through them passed fibroblastic and tenoblastic strands, which were making for continuity.

The graft (fig. 12 *D*) was recognizable as a remnant of tendon tissue which was blending in with the tissues surrounding it. From its ends long delicate fibrils and many nuclei were pushing proximally and distally to become lost in the fibrous and fibroblastic tissues that served to effect union. Mitoses were not seen in the graft itself nor in the fibrils, but from the large vesicular character of the

Fig. 11.—Photomicrographs of tissue intervening between the ends of the grafts and the stumps. *A*, in some places in T 5 the central area is merely an accumulation of red blood cells becoming infiltrated with white cells. In some places organization is beginning. The sheath (*Sh.*) from stumps and graft have bridged the defect. *B* (T 17, ten day specimen), the silk knot interferes with the organization of the intervening tissue (*Int. T.*), but the proliferated sheath helps to maintain union until organization is complete. *C* (T 15, eight day specimen), the organization of the intervening tissues takes place by the ingrowth of vessels and fibroblasts as well as by the ingrowth of tenoblasts.

nuclei and their great increase in number it must be assumed that the tendon cells had multiplied. There was considerable infiltration of this area with white blood cells.

The sheath tissues had been removed along one side of the graft. On the opposite side they were thickened, and the synovial lining was absent. Numerous blood vessels were present.

Microscopic examination of the distal stump revealed marked changes. There was great increase in the number of intratendinous vessels and of the cells of the peritenonium internum which stood out as thick cellular strips, breaking up the longitudinal arrangement of the tendon fibers. The sheath along one side of the tendon was quite vascular, moderately thick and made up of longitudinal strands of connective tissue. Study of the tendon showed numerous areas of degeneration through it, often fairly extensive necrosis, with white blood cell infiltration and replacement by proliferation from the cells of the peritenonium internum. Only in spots did one see any evidence of tenoblastic proliferation.

It was evident that the distal stump not subjected to pull was slowly degenerating and being replaced by scar tissue mainly of connective tissue origin.

Dog T 32 (fig. 5).—Transplantation of a 2.5 cm. graft into a defect of similar size in the extensor carpi radialis tendon was made and a cast was applied.

The dog was killed on the eighth day. The skin and superficial fascia were quite easily separated from over the graft area. Pull on the muscle above showed that the tendon was sufficiently united to extend the joint. There had been a 1 cm. separation at the distal suture line, but the ends were still held together by the suture. This pulled out, however, when a pull of 4 pounds (1.8 Kg.) was applied.

The microscopic section consisted of the proximal stump and a small bit of the graft still attached to it. The stump was recognizable as normal tendon in which few changes had taken place. It was covered on either side by a very dense sheath which included also the remaining bit of graft. Very few changes from the normal were apparent in the proximal stump, except in its distal end, where there was some nuclear increase and a proliferation of fibers from it which could be traced into the intervening tissues.

The sheath tissues were quite thick and vascular. Well developed, longitudinally arranged fibrous tracts ran through it.

The graft appeared viable, but no signs of cellular proliferation could be made out. (The sections were poor.)

Nine Days.—*Dog T 30.*—Transplantation of a 2 cm. graft of tendon plus its paratenon was made into a defect of similar size in the extensor carpi radialis. A very small and slender tendon was used as graft, and a cast was applied.

The animal was killed on the ninth postoperative day. The dog had died several hours before the tissues were fixed. There had been a 2.5 cm. separation at the proximal suture line, and the graft which lay near the distal stump looked soft and gray. Sections of tissue were removed from the stumps and graft for cross-sectioning.

Microscopic examination of the proximal stump showed some increase in the intratendinous connective tissue; otherwise, in the section studied (a cross-section) no notable changes were found.

Cross-sections of the graft showed most of it to be alive, with only here and there spots of degeneration. Certain peculiar areas containing giant cells were found, and were assumed to be degenerating bits of striated muscle included in the graft. We could make out no evidence of tendon cell proliferation. The sheath

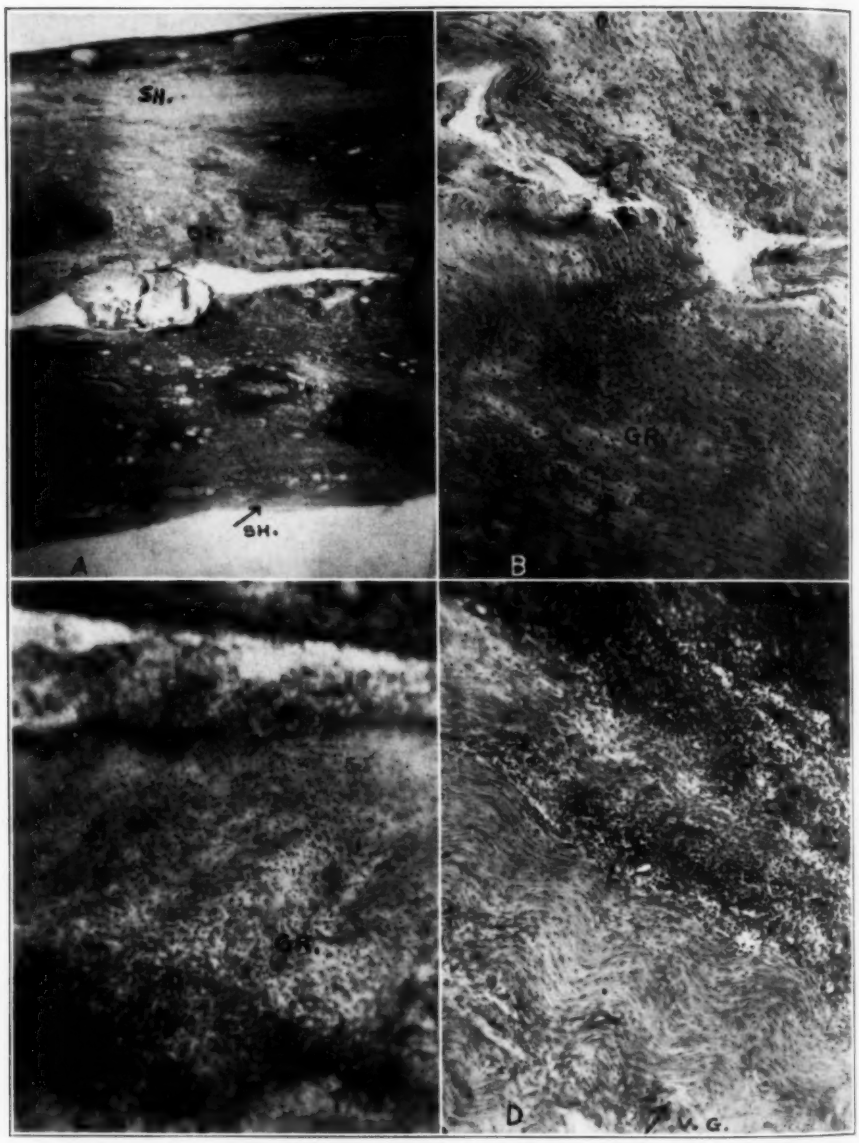


Fig. 12.—Photomicrographs of areas of graft tissue. *A*, *B* and *C* are of T 5, a ten day specimen; most of the graft has become necrotic and is infiltrated with white cells (*C*). *D* is of T 15, an eight day specimen; parts of the graft are still alive in this specimen. *V. G.* stands for viable graft.

tissues about the graft were thickened and quite vascular. There was no evidence of a synovial membrane about the tendon.

The tissue intervening between the graft and the distal stump contained a bit of silk about which there was inflammatory infiltration, and to either side of which (more marked along one side than along the other) was a band of quite nuclear and vascular dense connective tissue.

The distal stump had been very much broken up by the sectioning and showed merely a strand of silk contained in tendon tissue. These sections were very poor and were not of much value.

TEN DAYS.—*Dog T 5.*—Transplantation of a graft of tendon plus its sheath-tissue about 2.5 cm. long was made into a defect of the same length in the tendon of the extensor carpi radialis. Lacing sutures were placed in each stump, and the graft was threaded over a suture passing from stump to stump.

The tendon was removed on the tenth postoperative day. The whole mass formed a continuous, though rather bulky looking, tendon.

The microscopic specimen consisted of a longitudinal section of the replacement tendon, which was made up of the two stumps of the extensor carpi radialis bound together by a definite band of tissue which contained the graft. The graft itself lay much nearer to the distal than to the proximal stump.

The proximal stump (fig. 9 *A*) had been rather badly broken up by the suture material about which there was considerable round cell infiltration. Giant cells were seen occasionally among the round cells, but they formed no prominent part of the picture. The vessels and intratendinous connective tissue of the tendon were both increased throughout. The tendon tissue itself showed little change in its proximal part at the musculotendinous junction. More distally, however, the changes were striking. The tissue became much more cellular and was broken up by longitudinally running strips of dark blue-stained cellular tissue. Some of these strips were areas of cellular proliferation about the intratendinous vessels; others, however, appeared to have no relationship to the blood vessels, but had developed from the tendon itself. Study of the tendon through the distal part showed its nuclei to be fatter and more oval. The nuclei were increased in number, and mitoses were seen. As the end of the tendon was approached, the cells became more numerous, and the deep eosin-staining character of the collagenous material became less apparent. Mitoses were more frequent, and the tenoblasts appeared to push outward into the intervening tissue, where they became lost among the other cellular elements.

The sheath over the proximal stump was dense, thick and vascular. It pushed distally over either side of the stump and could be traced more or less continuously to merge indistinguishably with the sheath tissues about the graft.

In the region between the proximal stump and the graft the intervening tissues were represented by an outer layer of dense connective tissue which was traced from the sheath of the proximal stump to the sheath of graft (and incidentally to the sheath of the distal stump) and a central cellular reactive zone. In this zone were numerous leukocytes, red blood cells, fibroblasts and here and there long strands of connective tissue. This was a granulation tissue which was becoming organized. Security of union was due, however, to the outer layer of sheath proliferation.

A good deal of the graft (fig. 12 *A, B* and *C*) had disappeared or was necrotic and infiltrated with leukocytes; and a good deal of the tissue about it was organizing granulation tissue. However, its sheath tissues along one side (fig. 12 *A*) were thick and proliferated and were in direct continuity with similar tissues proceeding from (or at least in direct continuity with) sheath tissues of the two

stumps. Parts of the grafted tendon were still alive, and here were found the same evidences of tendon proliferation that were found in the proximal stump, i. e., increase in number of nuclei, increase in size of nuclei with assumption of a more oval and vesicular type of nucleus, mitoses, decrease in eosin-staining substance and tenoblastic proliferation into the intervening tissues.

Between the distal stump and graft was granulation-like tissue, presumably reaction about the silk suture (fig. 11 *A*), while on one side was a layer of connective tissue which afforded the effective union.

The tendon of the distal stump showed the same changes that were described in the proximal stump, i. e., increase in blood vessels, increase in intratendinous connective tissue and increase in sheath tissue. At its most distal end the stump had the appearance of normal tendon. More proximally, however, where it abutted the intervening tissue and for some little distance distal to this line, there were bands or zones running through it that showed cellular increases. Mitoses were seen scattered through the distal stump also, more numerous some little distance from the suture line itself, since right at the suture line there was some tendon necrosis.

Dog T 17.—Transplantation of a 1 cm. tendon graft was made into a 1 cm. defect of the extensor carpi radialis, and a cast was applied.

The animal was killed on the tenth postoperative day. The graft was seen to lie between the two stumps, united to them at either end by a gelatinous-like, soft-looking material which preserved the continuity of the replacement tendon (fig. 25).

From gross examination of the specimen one would suspect that the preceding sections of T 5 would be altogether different from those of T 17. As a matter of fact, there were the same histologic findings. Union was due to the sheath bridging over the defect (figs. 10 *B* and 8 *B*), while both stumps (fig. 9 *B* and *C*) were beginning to send tenoblastic fibrils into the intervening tissues. This soft gelatinous intervening tissue was microscopically the same as the more fibrous-looking tissue from the preceding specimen. More of the graft was viable than in T 5; there were here signs of proliferation, which were less marked than in the stumps. The reaction about the silk and the knots lying at the end of the graft formed some impediment to the penetration of these tissues by tenoblasts from the graft.

Dog T 33.—Transplantation of a very long segment of a small narrow tendon with its peritendinous tissues was made into a defect in the extensor carpi radialis tendon. A plaster cast was applied.

The animal was killed on the tenth postoperative day. The graft was found to have pulled away entirely at the distal suture line.

Most of the graft was alive and had preserved in many places the wavy course of its tendon fibers. Union between the proximal stump and the graft was due to the proliferated sheath. Histologic findings were the same as those for dogs T 5 and T 17.

Eleven Days.—*Dog T 4.*—Transplantation of a graft of tendon plus its sheath about 2.5 cm. long was made into a defect of the same length in the extensor carpi radialis. The graft was threaded over a double suture of grade D twisted silk, which was fastened by a lacing suture into each stump. The dog was killed on the eleventh postoperative day. The regenerating tendon was considerably longer than the original tendon, but it was continuous.

Microscopic examination on the eleventh postoperative day showed about the same picture as did the specimens previously described for the tenth postoperative

day. The two stumps were found to be separated by a considerable gap, the central part of which contained the silk, with organizing granulation tissue about it. To either side were strands of connective tissue which could be traced fairly satisfactorily from stump to stump and included the sheath tissue of the graft.

The stump showed more evidences of proliferation than were found in the preceding sections. There were large areas of tendon in which the nuclei were greatly increased in number, large, oval, pale and vesicular, throughout which mitoses were liberally scattered. These areas of proliferation occurred not only close to, but also at quite a distance from, the suture line. At the distal end of the proximal stump, tenoblastic fibrils were seen running outward to mingle with the granulation tissue.

Although about one half of the graft seemed to have disappeared, the rest of it was quite vascular. The parts that were alive showed tenoblastic proliferation.

Here, as in specimens at the tenth day, the stump and graft were taking active part in the regenerative process. Union, however, was due to sheath tissues.

TWELVE DAYS.—*Dog T 23.*—Transplantation of a 1.5 cm. tendon graft plus its peritendinous tissues was made into a defect left by removing 1 cm. from the extensor carpi radialis. The graft was threaded over two sutures, which were fastened by a lacing suture into the proximal and distal stumps. A cast was applied.

The animal was killed on the twelfth postoperative day. The stumps and the graft were found to have fused into a solid mass (fig. 25) which was adherent to the deep fascia. The union looked very strong, but its tensile strength was not tested.

Microscopic examination showed that the stumps and graft were united into a definite structure, in the formation of which the tendon tissue itself was beginning to play a quite definite rôle.

The stumps (fig. 13 *B* and *C*) were quite vascular; the vessels for the most part ran longitudinally through them, and divided them into longitudinal strands. There was considerable increase in the cells about these vessels. The proximal stump and, to a lesser extent, the distal stump, were more nuclear than normal through the whole extent, though more so where they abutted the intervening tissues. This nuclear increase was not general or uniform, but tended to occur in zones and strips. Where the end of the stump lay against the intervening tissues, the tendon had a feather-like edge from which fine fibrillar strips of tenobiasts projected into the granulation tissue, where they became lost. Mitoses were to be seen in the tendon throughout the very cellular areas.

The graft (fig. 16 *B* and *C*) showed changes identical with those found in the stumps. It was well vascularized and very little of it appeared to have become necrotic. Most of it had been converted into a cellular proliferating tendon, with, here and there, stretches of red, deeply eosin-stained, unchanged tendon. From either end, fibril-like strands of tenoblasts (fig. 16 *C*) were pushing outward toward the stumps and taking part in the organization of the intervening scar tissue.

The silk lying between stumps and graft was being healed into place by a definite organization of the granulation tissue about it. The fibers and cells in this granulation tissue were beginning to line up in long rows or strips parallel to the line of pull of the tendon.

The sheath tissues from graft and stumps (fig. 15 *A*) were seen to bridge across the defect areas and were made up of dense, longitudinally arranged bands of connective tissue.

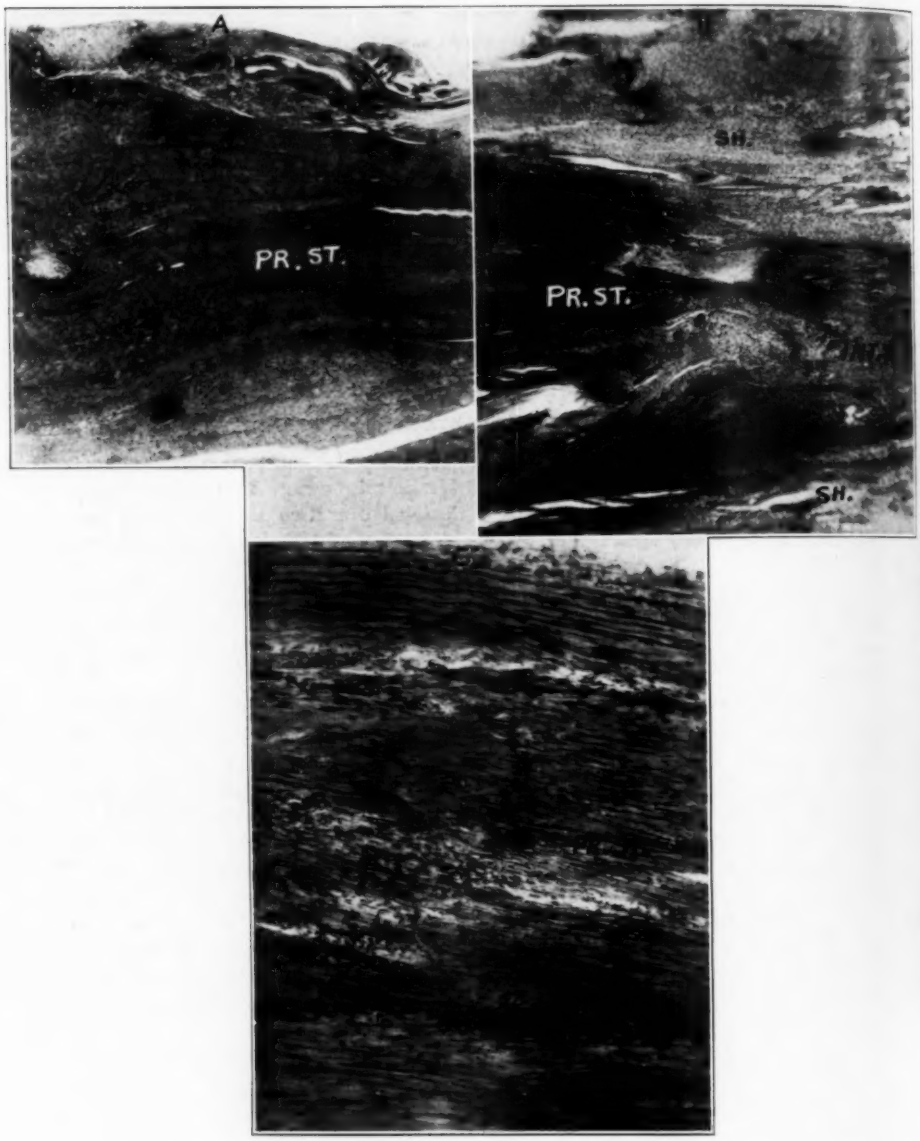


Fig. 13.—Photomicrographs of the proximal stump in a specimen removed from twelve to fourteen days after operation. *A*, the proximal stump (*Pr. St.*) of T 22 (fourteen days) shows the increased nuclearity of the tendon and the tendency for the fibers to straighten out. *B*, the proximal stump (*Pr. St.*) of T 23 (twelve days) tapers down into the intervening tissues (*Int. T.*) into which it sends proliferating fibers. The sheath (*Sh.*) has produced a thick dense union. *C*, under higher magnification the proximal stump (*Pr. St.*) of T 23 (twelve days) shows the characteristic increase in number of nuclei and blood vessels and the straightening of the tendon fibers.

When silk lay within the tendon it was sometimes surrounded by inflammatory cells, though in many places it appeared to lie directly against normal tendon or in an area of proliferating tendon. The silk itself was infiltrated with small round cells.

Fourteen Days.—*Dog T 22.*—Transplantation of a tendon graft plus its paratenon was made into a defect in the extensor carpi radialis. Apposition was good, but the graft frayed out a good deal. A cast was applied.

The dog was killed on the fourteenth postoperative day. The result looked quite poor; the distal suture line had separated, but the proximal suture line had held (fig. 25). Between the graft and the distal stump there was a good deal

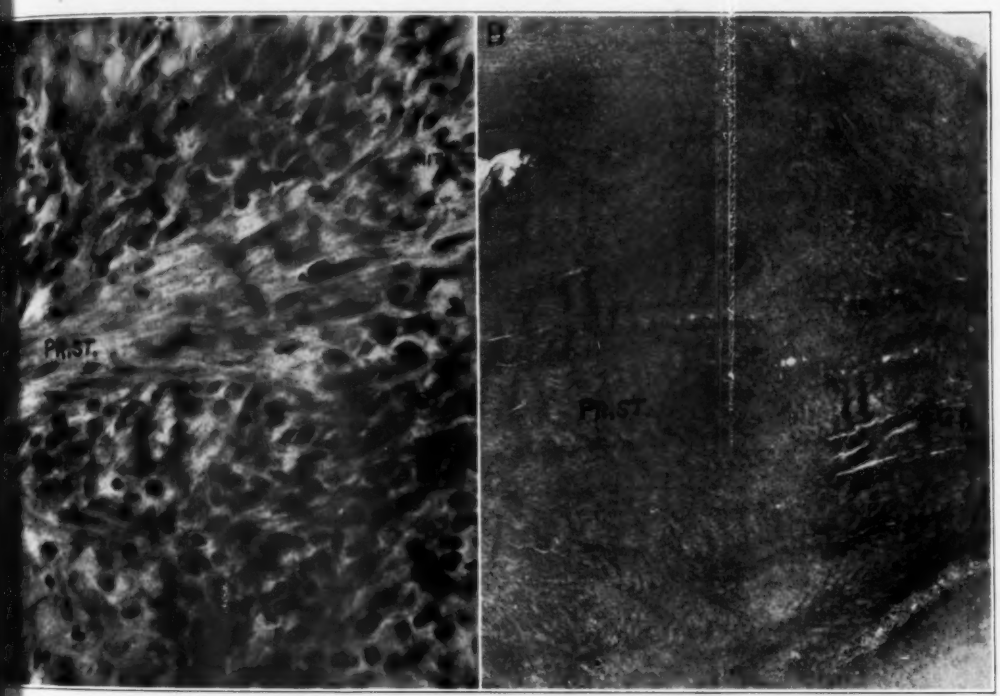


Fig. 14.—*A,* the distal end of the proximal stump of T 3 (ten days) is sending numerous long tender proliferations of tenoblasts into the intervening tissues. Mitoses (*Mit.*) are frequent. *B,* in instances in which the separation between the stumps and graft has not been too great (T 22, fourteen days), the union across the intervening tissues is already quite strong. A photomicrograph under higher magnification is shown in figure 12 *B*. *Pr. St.* stands for proximal stump, *Gr.* for graft.

of connective tissue, through which pull on the muscle was not transmitted to the distal stump.

Microscopic examination showed that, although there was a separation at the distal suture line, the union at the proximal line was excellent (fig. 14 *B*). Unfortunately, the section was mishandled during cutting, and the distal stump had been lost. The proximal stump and the graft were practically in apposition and were

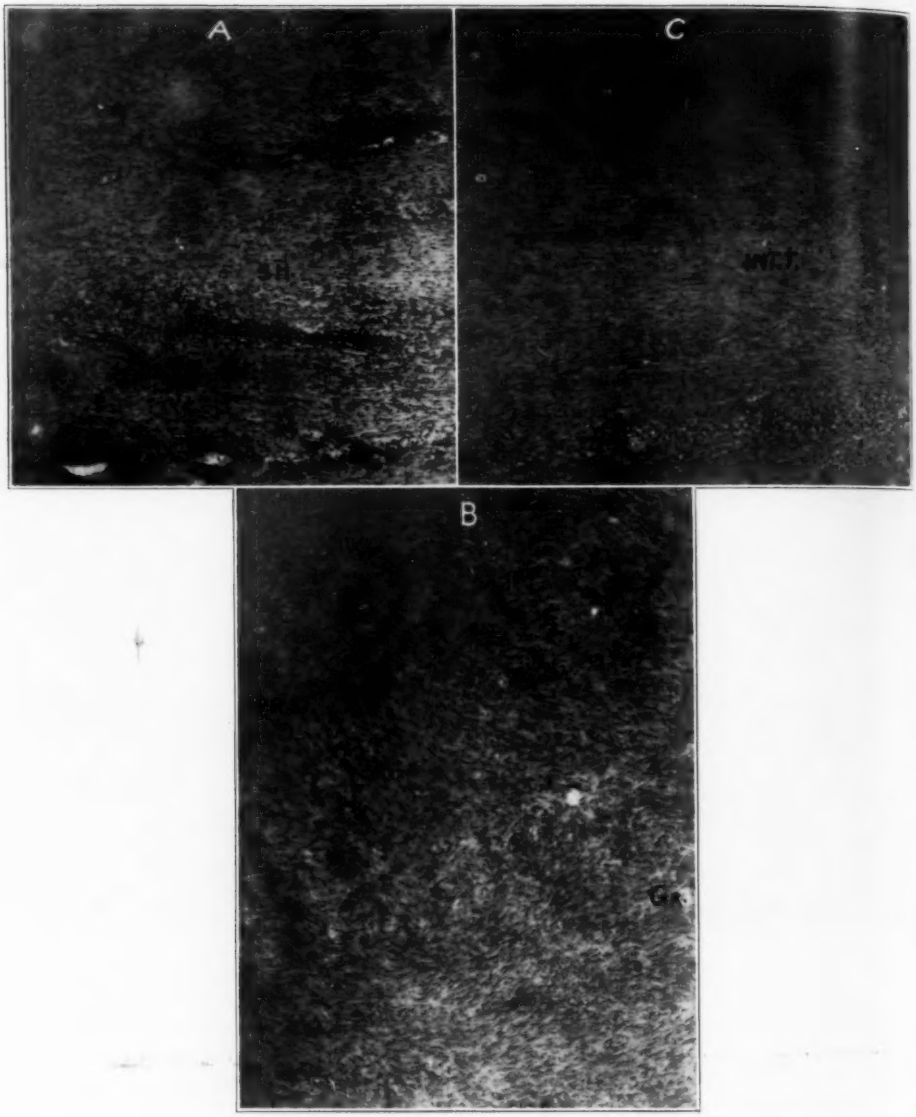


Fig. 15.—*A*, photomicrograph of the sheath over the intervening tissue in T 23 (twelve days). This is well organized and quite vascular. *B*, the tissue between the proximal stump (*Pr. St.*) and the graft (*Gr.*) in T 22 (fourteen days) have been solidly organized into a dense scar in which the tenoblasts from each tendon take part. *C*, the intervening tissue (*Int. T.*) of T 2 R (fourteen days) is organized into a dense tissue in which the fibers are arranged in long bundles parallel to the line of pull.

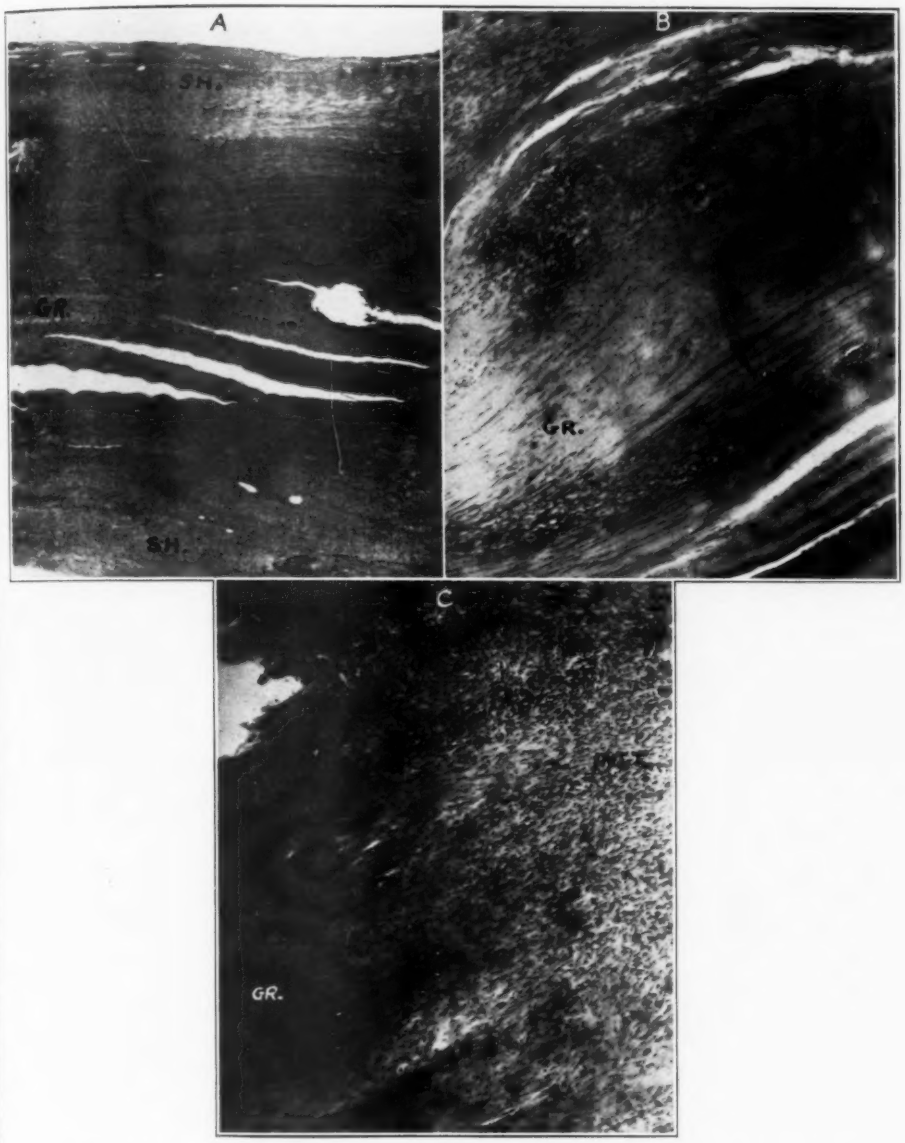


Fig. 16.—*A*, photomicrographs of the central part of the graft (*Gr.*) in T 22 (fourteen days), showing that it is practically entirely viable. Some of its fibers are still wavy, while others are straightening out. The sheath (*Sh.*) on either side is made up of longitudinally coursing connective tissue fibers. *B*, an area of the graft in T 23 (twelve days) showing the spotty character of the nuclear proliferation. *C*, the proximal end of the graft in T 23 (twelve days) is sending long prolongations of tenoblasts into the intervening tissues.

fused together solidly by a thin scar (figs. 14 *B* and 15 *B*) made up of tenoblasts proceeding from both graft and stump and of some granulation tissue. The proximal stump (fig. 13 *A*) showed nuclear increase throughout the length included in the section. This increase, as in previous sections, was not uniform, but occurred in bands throughout the tendon or in peculiar oval zones. One of these large zones was present several millimeters back from the end of the tendon and produced a definite widening of the tendon. The intratendinous vessels were increased, and the cells about them had proliferated. This proliferation about the vessels affected the peritenonium internum and the tendon itself. Considerable infiltration about the silk was present, but this was becoming organized, and a few giant cells could be seen in the tissues about the silk. From the end of the stump, rays of tenoblasts projected distally, some going directly toward the graft and there mingling with similar fibers from the graft, others passing to either side of the graft and ending in the proliferated sheath tissues.

The graft (fig. 16 *A*) appeared to have survived almost in its entirety and could not be distinguished histologically from the proliferating stump. It was quite vascular and appeared to be divided up into longitudinal zones by the numerous vessels which ran through it. There was cellular increase about these vessels. The nuclear content of the graft was increased, this increase, as in the stump, taking place in numerous zones or bands, running for a considerable distance throughout. These bands appeared (in stained section) much bluer than resting tendon, owing to the great nuclear increase in them. The silk had healed in nicely, though the tissue about the silk was not entirely fibrosed and still contained small round cells and giant cells. From the distal end of the graft, feather-like strands of tenoblasts pushed distally into the young fibrous tissue of the gap.

The sheath tissues in this specimen did not appear to be playing as important a rôle as they had formerly. There was very little sheath on the new tendon; it had presumably been split off in uncovering the specimen.

Dog T 2.—Transplantation of a segment of the extensor carpi radialis 3 cm. long, plus its sheath, was made into a defect of the opposite tendon. The graft was threaded over a double strand of silk, which was fastened by a lacing suture into each stump. No cast was applied. This procedure was carried out on the right leg.

The tendon (fig. 25) was examined fourteen days after operation. There was found a retraction of the stumps of about 1.5 cm. from each end of the graft. These spaces were filled with reddish-gray soft tissue that looked grossly like that in hematomas. The distal stump was slightly bulbous and had lost the pearly gray glistening appearance. There was some adherence of the sheath over the line of section. The proximal stump was also bulbous, and was soft and yellowish in appearance. Here too the sheath was adherent about the suture line. The graft was soft and lusterless. The hypertrophied sheath tissues appeared to bridge over the whole space between stumps and graft. On the under surface there was a dense band, probably mesotenon, running the whole length of the new tendon.

In this specimen, in which great separation had taken place, the manner of union differed from that in specimen T 22 of the same age. A considerable defect had to be bridged across, and here it was the sheath that had done it.

The stumps were separated approximately 3.25 cm. in the fixed specimen, and were united by a dense strand of very cellular and very vascular connective tissue which could be traced directly from the sheath tissues of either stump. This strand contained firmly embedded in its center a small bit of graft, about 0.4 cm. in length (fig. 25).

At the distal end of the proximal stump was an unorganized defect due to the knot in the silk. The stumps showed evidence of great proliferation, as evidenced by an increased number of blood vessels, an increase in nuclei and mitoses through the tendon and about the vessels. The nuclear increase was more marked nearer the suture line than away from the suture line. From the ends of the stumps proliferating strands of tenoblasts pushed into the intervening tissues to become lost in the fibrous and tendinous scar. The silk knot lying between the stump and the graft in the intervening tissue acted as a barrier to the tenoblasts.

The remnant of the graft showed increase in size and number of nuclei and the presence of occasional mitoses. From its ends there was proliferation into the connective tissues. The cells and fiber bundles of the graft were not as yet entirely oriented into a longitudinally arranged bundle.

The connective tissues forming the union (fig. 15 *C*) were arranged in longitudinal fashion, both fibers and nuclei, and in places it would appear that they were being divided into longitudinal bundles by blood vessels.

Dog T 29.—Transplantation of a 2.5 to 3 cm. tendon graft was made with satisfactory suture. A cast was applied.

The animal was killed on the fourteenth day. The superficial fascia and skin were easily dissected from the surface of the tendon; the proximal stump was conical and attached to the graft by a strand of silk covered with scar tissue. The distal stump was attached to the graft by a short stretch of silk also surrounded by scar tissue. The whole area was surrounded by thick strips of fibrous tissue which strengthened the union and were also somewhat adherent to the surrounding tissues. The strength of the union was tested by spring scale. The proximal stump pulled away from the end of the graft with a tension of 11½ pounds (5.2 Kg.).

Longitudinal section of the proximal stump showed a tendon of normal or resting histologic make-up in its proximal one-half. More distally, however, signs of proliferation were met with similar to those previously described. At the distal end of the stump the tendon fibrils pushed outward into the intervening tissues and mingled there with the connective tissue proliferation of the sheath.

The intervening tissue through which the rupture occurred (with a pull of 11½ pounds) was composed of condensed connective tissue which contained the silk suture. This connective tissue was still young and quite vascular. The tissue immediately surrounding the silk was organized, and the silk itself was infiltrated with small round cells.

An oblique longitudinal section taken through the graft showed this to be entirely viable. The silk lay in the tendon without any reaction about it and was infiltrated with small round cells. Except in the immediate vicinity of the vessels, and except for one area near one end of the graft, no evidence of tendon proliferation was seen.

A longitudinal section taken through an area of intervening tissues showed the silk suture embedded in tough connective tissue approaching the adult in type.

Sixteen Days.—*Dog T 3.*—Transplantation of a 1½ inch (3.5 cm.) segment of tendon graft plus its sheath was made into a defect left by removal of a ¾ inch (2 cm.) segment. The graft was threaded over silk which was attached by lacing suture into each stump. No cast was applied.

The graft was examined on the sixteenth postoperative day. The skin and superficial fascia were removed easily after a fairly definite plane of cleavage was found. The silk was not visible on the surface.

Microscopic examination represented an early stage (sixteen days) in the formation of a tendon scar in a graft experiment in which there had been considerable

separation of graft from stump. The graft had only partially survived and made up but a small section of the tissues lying between the stumps. (The picture was similar to that of T 2).

Union had been effected in the manner described in the section dealing with tendon suture. The sheath tissues to either side of the stumps had proliferated proximally from the distal stump and distally from the proximal stump and had united with the proliferated sheath of the graft.

Large areas of the intervening tissue and of the tissue about the graft were filled with organizing granulation tissue and areas of hemorrhage. Brown pigment deposits liberally scattered throughout the tissue were evidence of resorption of red cells.

Although a large percentage of the graft appeared to have died, other parts showed an increase in the number of nuclei. At the ends of the graft this cellular increase had led to the production of feather-like strands of tenoblasts which were pushing out into the granulation tissue, filling up the gap. Mitoses were to be seen among the tenoblasts.

The tendon in the stumps was considerably altered. Areas of necrosis were present near the suture line. There was, however, an increase in nuclei in the non-necrotic parts of the tendons, and from the ends of the bundles strands of tenoblasts radiated outward into the scar (fig. 14 *A*). The endotenonium was also sending fibroblastic bundles into the uniting scar.

This then, so far, was a sheath union owing to the great gap that had to be bridged over. Tenoblastic proliferation, however, was becoming quite evident.

Nineteen Days.—*Dog T 10.*—Transplantation of a 2 cm. tendon graft plus its sheath was made into a defect left by the removal of 1 cm. from the extensor carpi radialis. The graft was threaded over a silk thread which was attached to each stump by a lacing suture.

The dog was killed on the nineteenth postoperative day. There were no adhesions between the skin and superficial fascia and the underyling tendon. The distal stump was ruffled up as if too long for the space, and both stumps were slightly bulbous. The space between the stumps, measuring 3.5 cm., was bridged across by a small tough strand of white tendon-like tissue. The graft could not be identified as such, though in the center of this gap there was seen a yellow-white nodule of tissue which was thought to be a remnant of the graft. The tendon was quite adherent to the underlying bone, which had been stripped of its periosteum at the original operation.

The specimen examined microscopically followed in direct line those of dogs T 22 and T 23 and represented an excellent type of union in which both the stumps and the graft had taken part. Viewed casually, the whole regenerative tendon appeared to have a unified structure (fig. 26). Except for a short strip of resting tendon in the proximal stump, the whole of the tissues were very nuclear (fig. 17).

The whole of the tendon of the distal stump (fig. 17 *D*) was transformed into the highly nuclear young proliferating tissues that were seen in the earlier specimens. Mitoses were plentiful, especially as one passed from the distal end of the stump. The tendon was quite vascular. The passage from stump to intervening tissue to graft was almost imperceptible. It was possible to recognize the area of the graft only because of small areas of eosin-staining tissues.

The graft (fig. 17 *C*) was highly nuclear, and its strands of fibers were continuous at either end or at points that were assumed to represent the ends of the graft with fibers or cords of similar cells from the stumps.

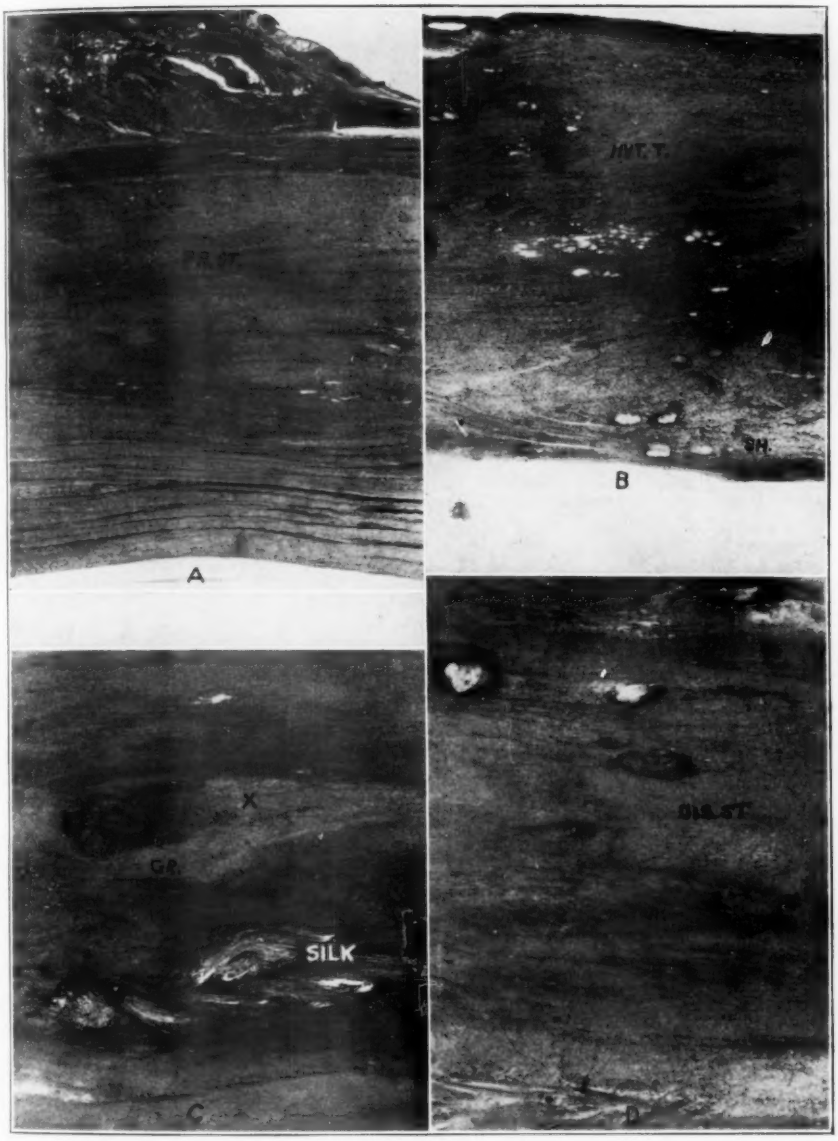


Fig. 17.—Photomicrographs through various areas of T 10 removed nineteen days after operation. The tissues are beginning to assume a remarkable sameness. *A*, the proximal stump (*Pr. St.*) is very nuclear; its fibers run in straight parallel lines and are divided into bundles by the intratendinous blood vessels. *B*, the intervening tissues (*Int. T.*) between the proximal stump and the graft are also lined up in long parallel rows. *C*, in the graft (*Gr.*) are a few areas (*X*) of the old deeply eosin-stained tendon. Most of it has undergone proliferative changes similar to those in the stumps. *D*, there has been somewhat less tendon proliferation in the distal stump.

The proximal stump (fig. 17 *A*) showed a small zone of nonreactive tendon, which, however, was more vascular than normal. The rest of the tendon had been converted into cellular proliferating tendon, from which strands passed distally into the intervening tissues.

All of these tissues, i. e., those of the stumps, intervening tissues and graft, were beginning to line up into longitudinally arranged bundles with blood vessels between them.

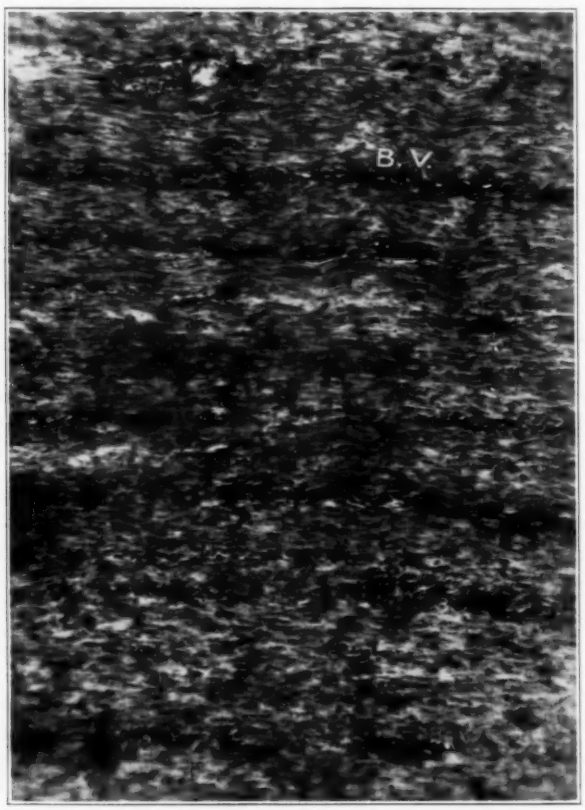


Fig. 18.—Photomicrograph of the tissue intervening between the graft and the proximal stump in T 18 (twenty-one days). The tissue made up of tenoblasts and fibroblasts is divided up into long parallel rows of very nuclear fibers by numerous longitudinal blood vessels.

Twenty Days.—*Dog T 20.*—Transplantation of a 3 cm. tendon graft was made into a defect of the extensor carpi radialis left by the removal of 2 cm. of tendon. The graft was threaded over the silk suture, which was fastened into each stump by means of a lacing suture.

The dog was killed on the twentieth postoperative day. Considerable infection had developed, and the specimen was not examined microscopically.

TWENTY-ONE DAYS.—*Dog T 18.*—Transplantation of a 3 cm. tendon graft plus paratenon was made into a defect left by the removal of 2 cm. from the extensor carpi radialis. The graft was sutured into place by lacing sutures at each end and similar sutures in each stump. A cast was applied. The dog removed the cast himself two days later.

The dog was killed on the twenty-first postoperative day. The wound had healed nicely. The skin and superficial fascia were easily stripped from the surface of the tendon. There was direct and functional continuity between the ends of the stumps (fig. 26). The silk was not visible on the surface of the tendon. In the proximal stump there were seen numerous long red longitudinal streaks in the substance of the tendon.

The specimen examined microscopically was clearly made up of the two stumps with the intervening graft. It was seen that the separation at the proximal and distal suture line had been minimal, probably not over 0.5 cm. at either end. The region between stumps and graft was filled up with tissue which was in direct continuity with stump and graft.

The graft in its central parts was made up of very cellular tendon, divided by numerous blood vessels into longitudinal rows of closely packed fibers. Defect areas produced by the silk suture material within the graft were becoming organized into compact scar tissue, in the formation of which the tendon was taking part. At the ends of the graft the tendon bundles stained more lightly and were very nuclear. Long strands of tenoblasts pushed proximally and distally into the gap tissue and could be traced across this scar until they became continuous with similar strands from the stumps. This gap tissue was more vascular and arranged in less orderly manner than the graft tissues (fig. 18). It was made up of ordinary granulation tissue, of tenoblasts from graft and stumps and vacuole-like areas evidently caused by the silk.

The stumps had been almost entirely converted into proliferating tendon. Only here and there were there to be seen strands of old tendon fibers, and these were more numerous in the parts of the stump farther removed from the suture lines, i. e., in the proximal part of the proximal stump and distal part of the distal stump. The stumps had been considerably disturbed by the suture material, but this was now well healed in, surrounded by scar tissue in places and in other places by the proliferating fibers of the tendon. Around and about the buried silk, the tendon fibers pushed distally or proximally out into the scar of the gap through which they could be traced to become continuous with similar fibers from the graft. There was a general longitudinal parallel arrangement of the fibers in the stumps. This was broken up, however, by the presence of the suture material. The blood vessels in the stumps were markedly increased, and this applied especially to the longitudinal ones which divided the stump into longitudinal bands.

The sheath tissues were somewhat thickened and were continuous over the stumps and over one side of the graft. The outer layers of the sheath were loose and very vascular and apparently were taking over gliding function.

In this specimen there was repair mainly due to direct union between stumps and graft. The sheath had proliferated, but was now beginning to take over gliding function. The scar between stumps and graft was made up of organized granulation tissue plus tenoblasts, and the tenoblasts were apparently the major part.

Dog T 19.—Transplantation was done as in the preceding experiment on dog T 18. A cast was applied and stayed in place.

The dog died on the twenty-first postoperative day. The wound was clean and dry. The skin and superficial fascia stripped very easily from the surface of the

graft and stumps. The stumps and the grayish graft were in strong functional continuity. Pull on the muscle led to extension of the radiocarpal joint, with a range of motion of 90 degrees. There was a lax paratenon arrangement about the whole new tendon which permitted good motion.

Microscopic examination showed that there had been a separation of about 0.75 cm. at each end of the graft. These gaps, however, were bridged across by fairly solid tissue which at one place had been broken up by the microtome knife striking the suture material during sectioning. The tissue consisted entirely of tendon and graft with uniting gap tissues, no sheath having been removed from the animal, which corroborated the note that a paratenon-like arrangement was present.

In the main, the parts of the stumps at some distance from the suture lines looked like normal adult tendon. The tendon might have been somewhat more vascular and more nuclear than normal, but it stained deeply with eosin, its nuclei were very flat and deeply staining, and it was arranged in long rows of parallel fibers. Where the silk passed through these apparently normal areas of tendon, it was infiltrated with round cells and surrounded by scar tissue. Back from the ends of the stump there was little reaction of the tendon itself about the silk. As the end of the stumps was approached, however, the tendon was much more nuclear, and the deep eosin stain disappeared, owing to decrease in the amount of intracellular substance and increase in nuclei. Fibers of the tendon ran into the scar tissue of the gap. The nuclei in the intervening tissue, however, were beginning to flatten out and to become more mature. It is evident that, with similar infiltration of the intervening tissues from the side of the graft, the gap was being converted into a dense tenoblastic and fibroblastic scar. The silk and the knot had become somewhat solidly encased in the scar, though here and there one could see giant cells about silk fibers.

A large percentage of the graft had survived and was actively proliferating. It had been rather badly broken up by the suture material, which, however, was well healed in place. The graft was quite vascular, but its tissues were not nicely lined up as yet, owing presumably to disruption due to the suture material.

Here again there was union due to healing together of graft and stump ends by a dense scar in which the tendon cells of both graft and stumps had taken part. The silk suture had caused a certain commotion in the structure of the scar.

Dog T 25.—Transplantation of a 2 cm. tendon graft plus its paratenon was made into a defect left by the excision of 1 cm. from the extensor carpi radialis. The graft was threaded over two silk sutures, which were then laced into the stumps. The graft was too long, and it wrinkled up after being sutured into place. A cast was applied.

The dog died on the twenty-first postoperative day, and postmortem examination was not made until the day following. The tissues could be stripped easily from the tendon. It was found that the suture had pulled out at the proximal suture line, and that there was a separation here of 3 cm. The graft was securely attached distally. The proximal defect was bridged with a thin scar which broke very easily on slight pull. No microscopic examination was made, since the tissues had been too long unpreserved.

Dog T 2.—Transplantation of a 1¼ inch (3.1 cm.) segment of tendon plus sheath was made into a defect of similar length in the extensor carpi radialis. The graft was threaded over a silk suture which was laced into each stump. No cast was applied. This procedure was carried out on the left leg.

The animal was killed on the twenty-first postoperative day. The tissues over the line of graft were bound to the operative area by dense adhesions which had to be removed by sharp dissection. Between the stumps, which had separated 4.5 cm., was a swelling which when opened was found to contain about 5 cc. of bloody fluid

and a few strands of white tissue. To the lateral side of this cavity and in direct continuity with it was another cavity in which the silk suture was found. The specimen was carefully removed and placed in formaldehyde.

Microscopic examination showed that considerable separation had taken place between stumps and graft, and a rather insecure union had been effected by a band of connective tissue along one side of the structure. The graft was definitely recognizable, was largely necrotic and was invaded by blood vessels and lymphocytes. Even in the most infiltrated areas, however, one could see large oval, vesicular, active, tendon nuclei with occasional mitoses as evidence of tenoblast formation.

The stumps were much more vascular and considerably more nuclear than the graft. This proliferation was most evident in the proximal end of the distal stump and the distal end of the proximal stump, where nearly the whole of the tendon was converted into a densely cellular structure. Further back from the suture lines the areas of cellular increase were distributed, bandlike, throughout the tendon. Along the side of the stumps from which the sheath proliferation proceeded, the tenoblasts tended to follow out somewhat along the line of tendon pull. Opposite this area, however, the arrangement of tendon nuclei was more irregular.

The proliferated and moderately thickened sheath was continuous from stump to stump, having fused with the thickened sheath tissues of the graft. The sheath was highly vascular, and only in places was it lined up in longitudinal parallel rows.

Twenty-Two Days.—*Dog T 1.*—Transplantation of a 1½ inch (3.8 cm.) segment from one extensor carpi radialis was made into a defect left by the removal of a similar segment from the same tendon on the opposite leg. The graft was threaded over a double strand of number D twisted silk, which was secured by lacing sutures into each stump. No cast was applied. Reciprocal graft was made into both legs, and the sheath closed carefully.

The animal was killed on the twenty-second postoperative day and both specimens were removed. On the left leg, the graft apparently had been replaced by scar tissue (fig. 26) in which a few fibers, apparently tendon, were still visible. The whole area was densely adherent and immovably bound down in scar tissue. Both of the stumps were bulbous, the distal more so than the proximal. The sheath over the stump appeared normal. On the right leg, the conditions were about the same, except that the adhesions were somewhat less marked.

Dog T 1.—The microscopic picture was complicated by the presence of the crossing tendon of the extensor pollicis longus. This had become embedded on the surface of the replacement tendon (Ersatzsehne [Schwarz]) and showed a moderate increase in nuclei. This procedure was carried out on the right leg.

Both stumps had been converted into very nuclear and vascular irregular bands of proliferating tendon tissue. The nuclei, which were so numerous that the tissue stained quite purple with hematoxylin, were oval and elongated, much fatter and more lightly staining than resting tendon nuclei. Mitoses were to be seen well scattered throughout the stump.

The nuclei were beginning to be arranged in longitudinal fashion, parallel to the line of pull, but the vessels were only beginning to show this longitudinal arrangement. The line of fusion between the stumps and the tissue uniting them was much less distinct than in any previous specimen. In general, the stumps were more nuclear than the intervening tissue. This scar of intervening tissue was made up of fibrous vascular connective tissue, plus prolongations from the ends of the stumps. It also contained the proliferating graft.

It was difficult to recognize the graft tissue definitely as such, owing to the complicating factor of the crossing tendon. Still there was one location in the unit-

ing tissues that presumably represented the graft. It was made up of very vascular bundles of fairly deeply eosin-stained fibers with numerous oval vesicular nuclei among which mitoses were to be seen quite similar to the proliferating tendon of the stumps. It too was being lined up in longitudinal bundles parallel to the line of pull.

Dog T 1.—Microscopic examination showed that here (the left leg) the differences between the various segments of the replacement tendon had almost disappeared. It was still possible to recognize the proximal stump as such, but the distal stump, graft and intervening tissues were blended into a unified whole. The differences between the proximal stump and the remainder of the tendon were more apparent on gross examination of the slide than they were on microscopic examination. A few strands of deeply eosin-stained nonproliferating tendon fibers were still visible, but most of the stump had been converted into bands, whorls and oval masses of very nuclear proliferating tendon. Where this proliferation was the most marked it had resulted in an increase in diameter of the tendon, hence its bulbous end. This bulbous end tapered down slightly and ran with practically imperceptible histologic change into the intervening tissues.

The proximal stump was quite vascular, the vessels, while running for the most part longitudinally, also ran to some extent transversely and obliquely across the tendon. Changes were beginning to appear in the nuclear areas of tendon. Some of these areas, those most deeply stained with hematoxylin, resembled those present in the earlier specimens, i. e., the nuclei were oval and fat, quite vesicular, and the eosin-staining intercellular material minimal. However, in the other areas, there began a flattening of the nuclei, an increase in the amount of eosin-staining intercellular material and a more adult appearance to the tissue.

The tissue between the stumps had taken on a uniform character. The location of the graft was still betrayed by the presence of a small area of deep eosin-staining fibers; otherwise the whole stretch was made up histologically much the same as the stumps. There were numerous blood vessels, running partly transversely and obliquely in the tendon, but the majority were longitudinal and were beginning to divide the tissue into longitudinal bundles. The nuclei throughout the central part were elongated, oval or cigar-shaped, vesicular and faintly staining. There was considerable eosin-staining substance making up the fibrous-like bundles of which the new tendon was composed.

Where silk lay in either the stumps or in the replacement tendon it was firmly embedded, though infiltrated with round cells. Occasionally, numerous foreign body giant cells were seen about the silk.

The sheath tissues had been removed at the time the specimen was excised. They separated easily and formed no integral part of the union.

Twenty-Five Days.—*Dog T 13.*—Transplantation of a 1.25 cm. graft was made into a defect of the extensor carpi radialis left by the removal of 1 cm. of tendon. The graft was threaded over a double strand of grade D twisted silk which was laced into each stump. No cast was applied. The sheath was not closed, and the area was covered by the superficial fascia.

The animal was killed on the twenty-fifth postoperative day. The area between the two stumps was filled by scar tissue which was adherent (fig. 26). A fibrogelatinous sheath appeared to be forming over the new tendon. This sheath, when opened, was found to be adherent to the connecting scar, but allowed a certain degree of motion through it.

The proliferating changes in and about this replacement tendon had been enormous, so that the resultant structure was very thick and broad. The graft

had been strung over a double strand of silk which was still visible. The stumps could still be identified as could also the region of the graft, but they were all becoming unified into a structural whole. Except for the great size of the tendon, the tissue had the same histologic characteristics as those just described for dog T 1 L.

Dog T 12.—Transplantation of a 1.5 cm. graft taken from one extensor carpi radialis was made into a defect left by removal of 1 cm. from the other extensor carpi radialis. The graft was threaded over a double silk suture which was secured by lacing suture into the stumps. No attempt was made to close the sheath, and no cast was applied.

The dog was operated on again twenty-five days after the graft was made. The result was poor. There were massive adhesions between the skin and tissues between the stumps. The area between the stumps was replaced by a scar in which the suture was embedded. The suture had pulled out from the distal segment, but was still attached proximally.

Microscopic examination showed that in this specimen the proliferating changes in the proximal stump were marked, though there had been a good deal of disruption here owing to the silk, which was, however, firmly embedded. The gaps between the stumps and graft had been quite large, but they were successfully bridged across by proliferation on the part of each stump and graft so that there was direct continuity between graft and stumps. The nuclei throughout were beginning to flatten out somewhat, but were still numerous. Only rarely were mitoses seen. The alinement in general was parallel to the line of pull, but this was not so well arranged as in other specimens.

Twenty-Eight Days.—*Dog T 9.*—Transplantation of 2 cm. of tendon graft plus sheath was made into a gap of 1.9 cm. left by removal of 1 cm. from the extensor carpi radialis. The graft was threaded over a double strand of silk which was secured into each stump by lacing suture. The sheath was closed, but no cast was applied.

The animal was killed on the twenty-eighth postoperative day. There was a small healing ulcer over the incision which was slightly adherent to underlying structures, but not adherent to the area of the graft. The stumps, which were separated 3.5 cm., were united by a thin rounded strand of tissue, which, however, did not look like graft. The distal stump was white and ruffled up somewhat as if too long for its space. The proximal stump was bulbous and tapered off into the intervening tissues. The whole area was densely adherent to the underlying bone, but not adherent to superficial fascia.

Microscopic examination showed that healing had taken place despite the ulcer on the leg. However, the presence of infection had complicated the picture considerably. The graft had only partially survived the ordeal. Both stumps and the graft, however, were proliferating despite the great amount of organizing granulation tissue that was surrounding them, and union had been secured.

Thirty-One Days.—*Dog T 28.*—Transplantation of a graft about 2.5 cm. long plus its paratenon was made into a defect of the extensor carpi radialis. The graft ends were secured in the stumps by means of lacing sutures. The sheath was not closed. A cast was applied.

The leg was reopened thirty-one days after this operation. A successfully functioning tendon was present (fig. 19). The stumps were bulbous, swollen and grayish. They were united by a bulbous strand in which the graft was undoubtedly embedded. There had been some separation at each end, but the amount could not be determined, since the ends of the tendon could not be ascertained. The tendon

pulled easily through the surrounding tissues and was subjected to a pull of slightly more than 40 pounds (18.1 Kg.) before rupturing. The break took place through the junction of the graft with the proximal stump.

Microscopic examination of a cross-section of the distal stump in this instance showed that the tendon was more nuclear than normal, although this increased nuclearity was by no means uniform. One large bundle making up one third of the tendon was hardly distinguishable from normal adult tendon, except for an increase in cells about the intratendinous vessels and an increased number of these vessels. The silk lay embedded in a narrow zone of connective tissue, infiltrated with small round cells, while here and there giant cells were seen about it. All of the tendon was more vascular than normal, and it was possible to trace small vessels from the surrounding sheath into the superficial surface of the tendon. Mitoses were still present in the area of tenoblastic increase, but were much less frequent than in earlier specimens. The sheath appeared to have been very loosely connected, since it had been practically all removed.

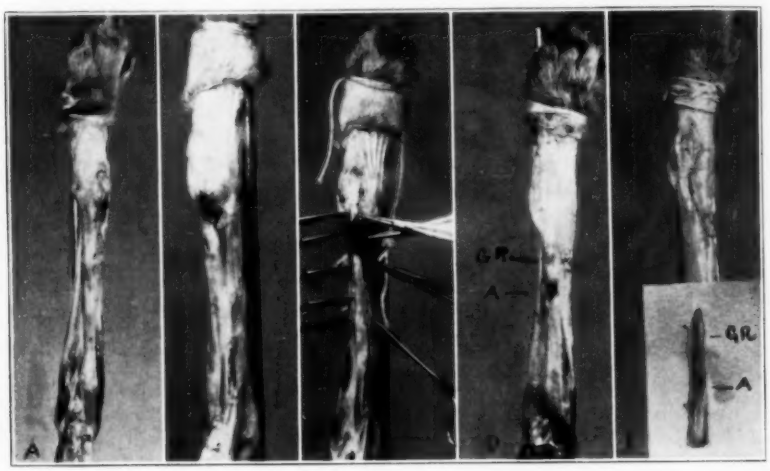


Fig. 19.—Gross specimens removed thirty-one (*A*, T 28), thirty-three (*B* and *C*, T 31) and thirty-five (*D* and *E*, T 27) days after operation. The sheath has been dissected away from T 28. In the first specimen of T 31 (*B*), the sheath is shown still covering the tendon; in the second photograph of this specimen tendon. In the first photograph of T 27 (*D*), the proximal suture line at point marked *A* shows up as a dark area, owing to its vascularity. This tendon ruptured at 36 pounds (16.3 Kg.) pull, not, however, through the rather weak looking suture line, as shown in the second photograph (*E*) of the specimen.

A cross-section of the graft showed it to be made up almost entirely of young or proliferated tendon. Only here and there were areas of old normal adult tendon to be seen. The striking feature of the section was the exact delimitation of the regenerating or replacement tendon. It lay as a separate definite entity of uniform histologic make-up, quite distinct from the surrounding sheath tissues. Although this sheath was connected with the replacement tendon of the graft along a good deal of its circumference, one particularly large strip of tissue was entering the tendon from the sheath, which reminded one of a mesotenon. Mitoses could be seen in moderate numbers in the graft.

The proximal stump had been entirely converted into proliferating tendon, and was made up of areas of very nuclear tendon bundles, for the most part cut transversely, though some were cut longitudinally and obliquely. Mitoses were present, but were not so numerous as in earlier sections, and the nuclei did not appear to be so large. The sheath surrounded the tendon as a distinct structure, more vascular and more loosely constructed. The synovial layer between sheath and tendon was not apparent, but a paratenon arrangement evidently accounted for the mobility. The suture was firmly embedded, and along the periphery was invaded here and there by strands of cells.

THIRTY-THREE DAYS.—*Dog T 31.*—Transplantation of a graft slightly over 3 cm. long was made into a similar defect in the extensor carpi radialis. The graft was secured to the stumps by means of lacing sutures. The sheath was not closed. A cast was applied.

The animal was killed on the thirty-third postoperative day. There was found a well developed fibrous sheath through which the graft moved easily, and which could be dissected away as a separate distinct layer from the underlying new tendon (fig. 19). Both stumps were enlarged and bulbous. They were firmly united to the graft by short segments of solid tissue (there had been a slight separation at each end of the graft). A pull of 35 pounds (15.9 Kg.) broke through the graft at the distal suture line.

Microscopic examination of a specimen showed that the three segments of the replacement tendon were present as three bulbous enlargements, each of which contained some areas of adult tendon, though made up mainly of proliferating tendon.

The gap between the proximal stump and the graft was bridged by a rather narrow strand of tough tendon-like tissue, in the center of which a length of silk lay embedded. The silk had been broken out by the microtome knife during sectioning and hence had left a long defect.

There was no line of demarcation between the graft and stumps and this intervening tissue. The fibers from the tendon of each structure passed directly over into the intervening regenerated tendon.

The nuclei in the proliferating parts of the tendon (fig. 20 *A* and *C*) were flattening out, though they were still more oval and larger than in normal adult tendon. Parallel longitudinal arrangement was present in the fibers making up the intervening tissue (fig. 20 *B*) as well as the proliferating areas in stumps (figs. 20 *A*, 21 *B* and *C*) and graft (fig. 20 *C*).

The suture material in the tendon was solidly healed in, and infiltrated slightly with round cells. At the point of rupture of the tendon at the distal suture line, the silk had made a large central defect in the replacement tendon. The tissues passing to either side of the silk were neither so dense nor so heavy as at the proximal suture line. Only thin strands of tendon fibers could be traced through it from the graft.

THIRTY-FOUR DAYS.—*Dog T 7.*—Transplantation of a 2 cm. length of extensor carpi radialis plus its sheath and mesotenon was made into a 1.8 cm. gap left by the removal of 1 cm. from the opposite tendon. The graft was threaded over a double strand of number D twisted silk which was secured into the stumps by lacing sutures. The sheath was carefully closed over the area by fine silk sutures.

The animal was killed thirty-four days following the operation. There was an ulcer over the incision, but this was lateral to the graft. The superficial fascia was stripped easily from the area of operation. There was separation at each end of the graft. The proximal stump had retracted considerably, the muscle belly

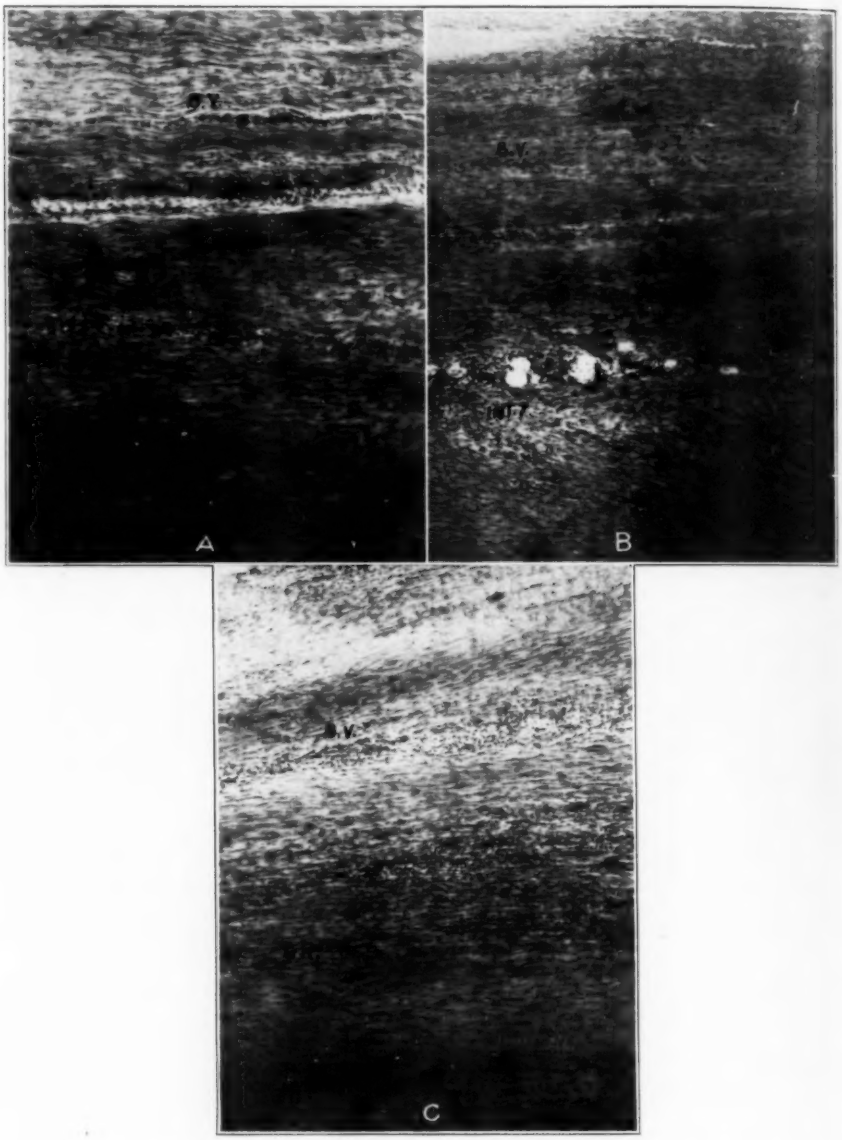


Fig. 20.—Photomicrographs of tissue removed from T 31 (thirty-three days). *A*, an area in the proximal stump (*Pr. St.*). The tendon nuclei are increased in number, but are flattening out. The intratendinous blood vessels (*B. V.*) are numerous, and there is an increase in cells about them. *B*, tissue intervening (*Int. T.*) between the proximal stump and the graft. It is also lined up in long parallel rows with numerous blood vessels. *C*, an area of the graft (*Gr.*) which shows the longitudinal arrangement of the tendon fibers, their increase in nuclei and the nuclear increase about the blood vessels.

was smaller than normal and appeared atrophic. The distal stump was grayish-white and ruffled up. The stumps were united by dense scar tissues adherent to the bone; in the center lay the graft.

THIRTY-FIVE DAYS.—*Dog T 27.*—Transplantation of a tendon graft plus paratenon was made into a defect of the extensor carpi radialis. The graft was secured by lacing suture into each stump. The sheath was not sutured; a cast was applied.

The animal was killed on the thirty-fifth postoperative day. The resultant tendon (fig. 19) functioned excellently. After all other tendons capable of extending the foot had been cut, the new tendon could completely extend the joint by pulling on the muscle belly. The graft appeared viable, lay in place between the stumps, and was securely attached to them. About the whole area were sheets of connective tissue which could be easily stripped from the tendon and which

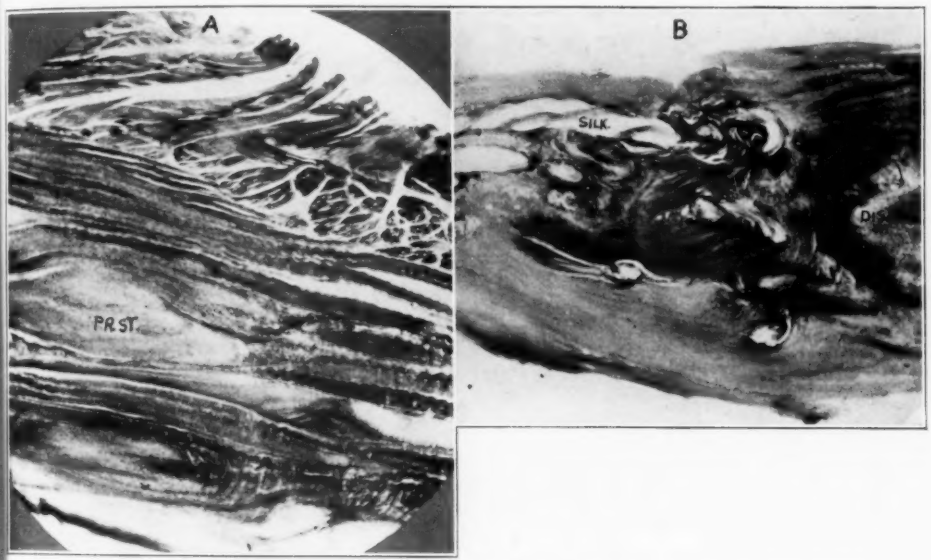


Fig. 21.—Low power photomicrographs of the proximal stump, *A*, and distal stump, *B*, of T 31 (thirty-three days). In the proximal stump the straightening of the fibers is well shown. In the middle of the stump is seen a large oval area in which tendon proliferation has been especially rapid. In the distal stump the silk has caused considerable disturbance of the tendon fibers, but the area here shown is well organized.

allowed very free movements. Before these sheets were separated from the tendon, a pull of 50 pounds (22.7 Kg.) failed to rupture it. After the surrounding paratenous tissues were divided, a pull of 36 pounds (16.3 Kg.) broke the tendon at the junction of graft and distal stump.

Microscopic examination of a cross-section of the proximal stump showed that the tissue was divided into a number of bundles practically all of which were cut exactly transversely, in comparison to earlier specimens in which, on cross-section, the section was seen to pass obliquely or evenly longitudinally through some bundles. Only here and there were very small areas of adult tendon seen; practically the whole section was a younger tendon, very nuclear. The nuclei were

oval or round, not so large and more darkly staining than in earlier stages of proliferation. Mitoses were not seen. The intratendinous connective tissue septums were quite thick in places. The sheath was a distinct paratenon-like structure and loosely bound to the tendon. There was no synovial membrane.

Cross-sections through the graft presented essentially the same picture as did the proximal stump. The blood vessels running through the graft were more numerous than in the stump. There were several areas in which gaps in tendon tissues were being filled with organizing granulation tissue.

The sheath was a perfectly distinct paratenon-like structure with a suture embedded in it at one place. The suture here was surrounded by granulation tissue containing giant cells.

The distal stump was also made up of very cellular bundles of fibers, cut for the main part transversely. It was more nuclear and arranged with less order

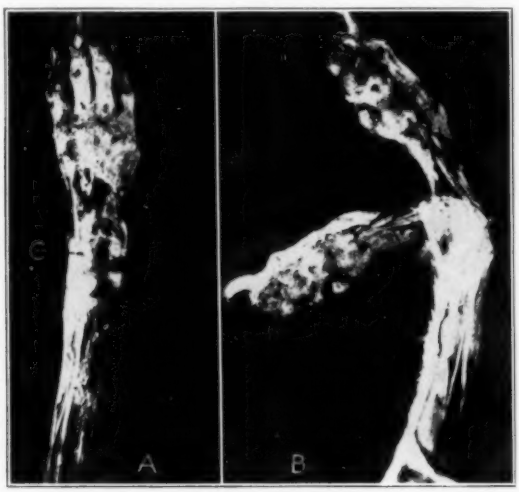


Fig. 22.—Photographs of the gross specimen T 11 (one hundred days). The replacement tendon is well shown in *A*. In *B*, the function of this tendon is shown by laterally superimposed exposures. *C* stands for replacement tendon.

than either the graft or the proximal stump. The sheath surrounding it was quite distinct from the tendon, though no synovial membrane was present.

Seventy Days.—*Dog T 16.*—Transplantation of a 2 cm. graft plus paratenon was made into the gap of the extensor carpi radialis left by the removal of 1.5 cm. of tendon. The graft was laid in place by side-to-side suture. The defect was longer than the graft, and the distal suture line was bridged by sheath. No cast was applied.

The dog died seventy days after operation. There was purulent arthritis of the radiocarpal joint, and a large encapsulated bag of pus lay under the area of the graft. The distal suture line had separated entirely. The proximal suture line still held, but the stump and graft were pushed ulnarward by a collection of pus.

Microscopic examination showed that, despite the infection, parts of the graft had survived, so that in its area was a large bulbous enlargement, made up of proliferated graft plus the organization of exudate. The proximal stump and

graft were firmly united by a strand of tissue which was quite thin in its central parts, but which broadened out at each end where it approached and became continuous with the stump or graft.

The tendon of the graft and the replacement tendon were very vascular and very nuclear. They were made up of long parallel strands of nuclear tissue (tendon), in which the fibers and nuclei were lining up in a direction parallel to the line of pull. Evidently, despite the abscess and arthritis, the tendon was pulling against some distal attachment.

Nothing of the distal stump was recognized.

One Hundred Days.—*Dog T 11.*—Transplantation of a 2 cm. length of extensor carpi radialis plus the sheath was made into a gap left by the removal of 1 cm. from the opposite extensor carpi radialis. The graft was threaded over a double strand of number D twisted silk, which was secured to the stump by lacing

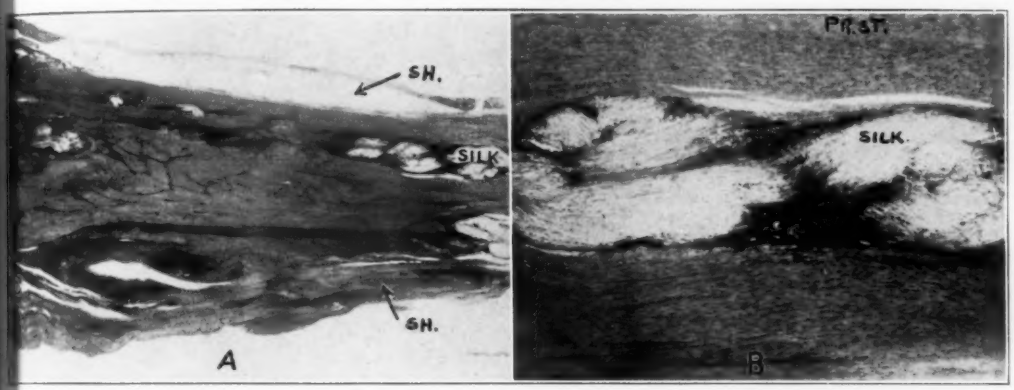


Fig. 23.—Photomicrographs of the proximal stump of T 11 (one hundred days). *A*, under low power magnification, shows the great vascularity of the proximal stump and its dense organization. The silk here has been well incorporated into the stump. The sheath along one side is thin and loose, along the other side thick. *B*, an area of the proximal stump under higher magnification. The silk is infiltrated with white cells, but there is no growth into it of tendon fibers.

sutures. The sheath was carefully closed over the suture lines. No cast was applied.

The dog was killed on the one hundredth postoperative day. He had excellent function in the leg on which operation had been performed. The skin and fascia were stripped from the replacement tendon with ease. The muscle belly was red and but slightly smaller than normal. Over the area in which the graft had been placed was a strand of silk, firmly embedded in dense white tissue. Overlying the whole area were thin fibrous sheets which were very lax and allowed the replacement tendon to move freely (fig. 22). The knot was seen in the distal stump about 1.5 cm. from its end.

Microscopic examination was made. The specimen (fig. 26) was a unified whole, showing the same histologic structure throughout, so that it was not possible

to distinguish graft from stumps and intervening tissue. It was made up of long continuous strands of dense tendon tissue (figs. 23 and 24), between which ran longitudinal blood vessels. The tendon fibers ran a straight parallel course for the most part, except when they passed around silk suture material. The nuclei were thin and flat, parallel to each other and to the course of the tendon fibers. Blood vessels were plentiful, not all of them longitudinal, but, in the regions of the stumps, transverse as well. The silk lay firmly embedded, infiltrated with small round cells. There was no longer any reaction around it.

The sheath had been removed, but there was no evidence of synovial membrane on the surface of the tendon.

The ends of this new tendon were somewhat bulbous in contrast to the narrow central part; this was the only suggestion of the one time location of the stumps. It was not possible to say whether the graft had survived or not.

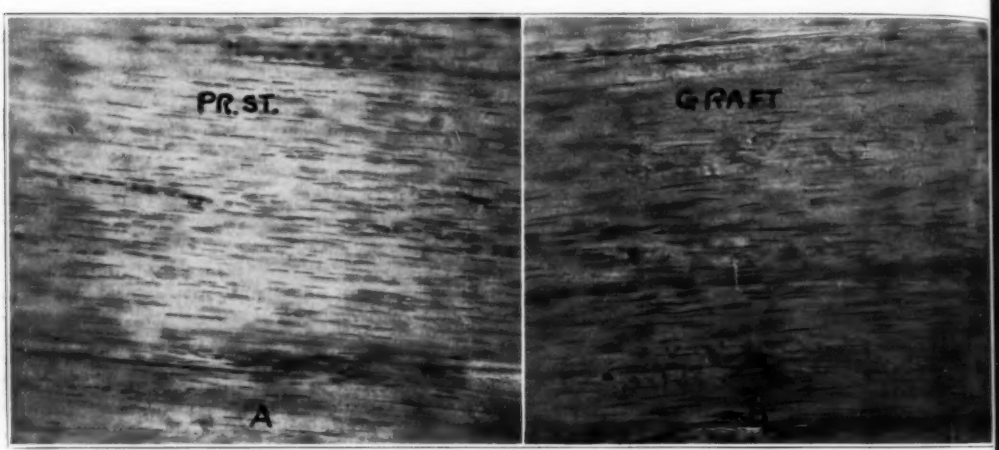


Fig. 24.—Photomicrographs under high power magnification of the proximal stump, *A*, and the region of the graft or replacement tendon, *B*. It is practically impossible to distinguish these areas from each other microscopically.

THE PROCESS OF REPAIR IN A TENDON GAP BRIDGED ACROSS BY A TENDON GRAFT

Microscopic study of specimens of tendon graft reveals an interesting course of events. Although the basic histologic process is the same in both the simple end-to-end suture and in the graft, the presence of a tendon graft in the defect is seen to play a definite rôle in healing.

Fourth to Seventh Day.—In a specimen removed on the fourth day after operation (fig. 4), the stumps and graft are united by the silk suture material over which there is proliferation of sheath tissues from each end, so that the gap is bridged across both by silk and living tissue. The sheath proliferation at this early stage is fibroblastic and is not yet sufficiently strong to take on the function of the tendon. The tendon

tissue in the graft is alive, but shows as yet no evidence of proliferation. There is some necrosis about the silk as it lies in the tendon, and there are irregular defects in the tissue. There is very little proliferation at this early stage about the intratendinous tissues of the graft. In the stumps, however (fig. 4 *C*), the intratendinous tissue (peritenonium internum) has proliferated, and at the place marked *x* in the illustration there is seen quite a wide strip of proliferating tissue which is pushing outward from between the tendon bundles into the intervening tissues toward the graft.

Eighth Day.—By the eighth day, the tendon stumps and graft are solidly fused together by thick strands of connective tissue (fig. 5), which make the newly reorganizing tendon look very thick and heavy. Important changes are taking place at this time. The stumps and graft are surrounded by sheets of tissue which can be separated from them only by sharp dissection. They appear to form an integral part of the new tendon at this stage.

The most important factor leading to union at this time is the sheath proliferation. In figure 6 *A*, which shows the proximal suture line at the seventh postoperative day, the distal end of the proximal stump is shown at *Pr. St.*, and the proliferated sheath at *Sh.* In the earlier stage, the thickened sheath was made up mainly of irregularly arranged fibroblasts; in this specimen the sheath tissue is beginning to arrange itself into long lines and bands of connective tissue fibers which run for considerable distances over the stumps and graft. This longitudinal arrangement is nicely shown in figure 6 *C*. At the suture lines, these connective tissue strips bridge across the defects and directly unite stumps and graft. The sheath proliferation and union are particularly striking if the sections pass through a silk knot lying between stump and graft, as is seen in figure 6. Here the defect presents itself as an actual absence of tissue, while to either side the thickened sheath insures union. Also where the stump and graft have separated, we find that the sheath tissues dip into the gap and play an important part in its organization (figs. 6 *A* and 7 *A*).

Changes begin to appear in the tendon tissue itself about the seventh day. Along with the proliferation about the intratendinous vessels, which has been noted in the earlier specimen, the tendon nuclei are beginning to increase in number. This increase is particularly marked in the ends of the stumps and the ends of the graft (figs. 6 *A* and 7 *A*). The closely approximated tips of the stumps and graft in a specimen stained with hematoxylin and eosin stand out as dark blue zones. From the ends of these zones, feather-like strands of cells push out into the intervening tissues. Throughout these zones and for a distance up and down throughout the tendon, there is noted a considerable increase in

the number of nuclei, which are becoming larger and more vesicular in character. Instead of the rod-shaped nuclei, which are seen in resting tendon (e. g., many of the nuclei in fig. 7 *B*), they are becoming more and more oval or even round and numerous mitoses are present, especially in the tips of the stumps (figs. 7 *C* and 8 *A*). It is especially interesting to note that the graft shows the same proliferative changes as the stumps. The central parts of the graft exhibit areas of necrosis that tend to become more numerous and of greater extent as the distal end of the graft is approached.

The intratendinous blood vessels, especially in the proximal stumps (fig. 7 *B*), are increased in number, and there is an increase in cells about them. At the ends of the tendon, the tissues from about these vessels send cords of cells into the intervening tissues (fig. 7*A*).

There is considerable inflammatory infiltration in the sheath tissue as well as in the tendon itself.

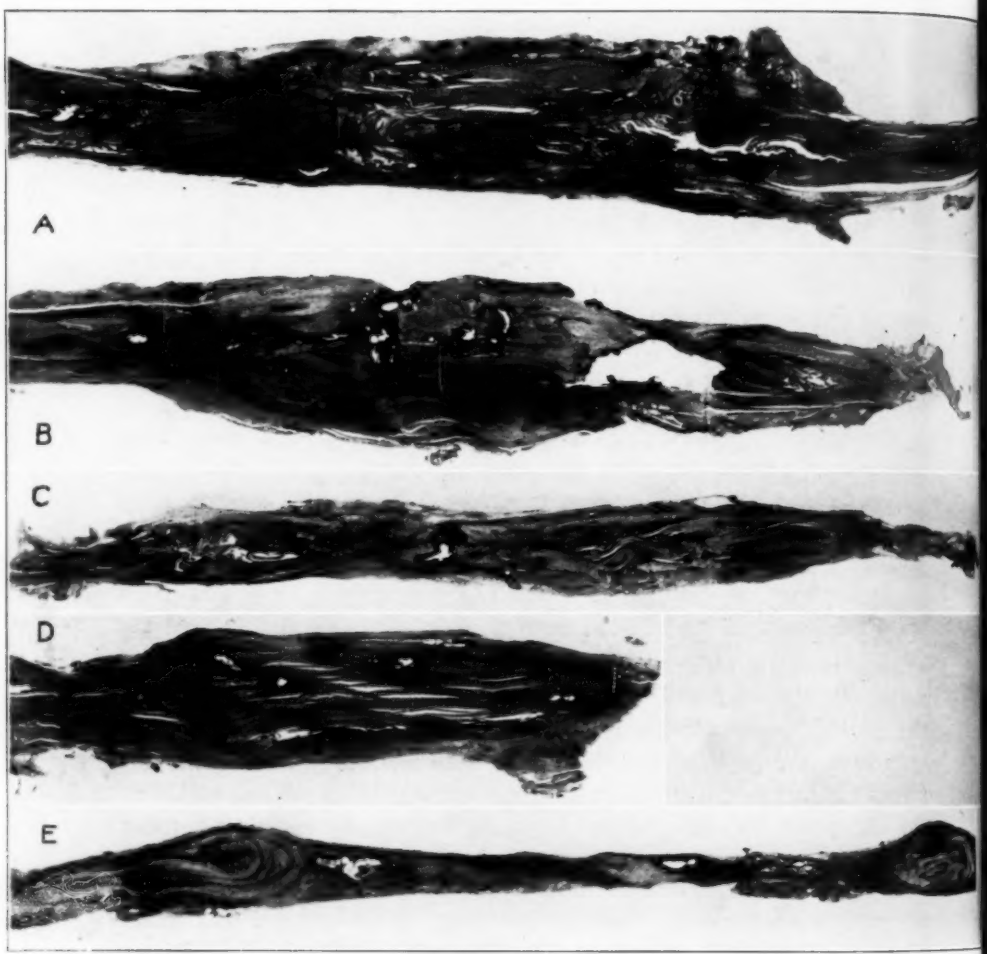
Eighth to Tenth Day.—From the eighth to the tenth day (figs. 9, 10, 11 and 12), the processes noted in their incipiency are becoming more distinct. The tendon proliferation from the stumps, more particularly from the proximal stump, is progressively infiltrating the tissues lying between it and the graft (fig. 9 *C*). Long fibrils may be traced from the tendon into the intervening tissues, where they become lost in the organizing scar. The nuclei throughout the tendon of the stumps, especially in the ends and in irregular zones throughout its length are increased in number, and mitoses are frequent. The clefts between the separate tendon bundles at the ends of the stumps are widened by an increase of cells about the intratendinous vessels. From these clefts, bundles of cells push out and take part along with the tenoblasts in the formation of the scar. In the parts of the stump that contain the silk, considerable defects are seen (fig. 9 *A*). About the silk and in these defects is considerable inflammatory infiltration (fig. 9 *A* and *B*). Where silk suture material lies at the end of the stump (fig. 9 *B*), it forms a barrier to the infiltration of the tenoblasts, although the cells push out on all sides of and beyond the silk. As in the earlier stages, tendon necrosis about the silk and inflammatory infiltration in the tendon are seen. The effective union at this time is due to the sheath tissues (fig. 10) which are becoming definitely organized into dense connective tissue in which the fibers are arranged in long rows parallel to the line of tendon pull (fig. 10 *A*). The nuclei of the sheath are beginning to flatten out and assume the character of adult fibrous connective tissue nuclei. The tissues of the sheath are still very much permeated with white blood cells, which in many places (fig. 10 *A*) are accumulated into fairly large foci. In places where the pulling out of the silk has resulted in the production of large defects (fig. 10 *B*), the importance of sheath union is especially striking.

During the first eight to ten days, the tissues lying between the ends of the stumps and the graft (i. e., the intervening tissues) are not so well organized in some specimens as in others. Thus, when the samples of intervening tissues taken from three different specimens of approximately the same age are contrasted (fig. 11 *A, B* and *C*), it is seen that in one the whole area is little better than an abscess cavity or a hematoma (fig. 11 *A*), while in another there is seen the most delicate of beginning granulation tissue (fig. 11 *C*). In the central specimen of this group (fig. 11 *B*), the silk has so disrupted things that organization about it would be very slow and difficult. These only serve to emphasize again the importance of sheath union in the early stages. In contrast to these poorly developed areas of organization is the intervening tissue at the distal end of the proximal stump, as shown in figure 9 *C*; here the tissue is dense and strong and contains numerous tenoblasts from the proliferating stump.

It might be noted here that examination of numerous specimens at various stages shows an extremely varied histologic picture. It is very difficult to assign any day by day chronology to any series. It is only by the examination of a large number of sections that a chronologic picture can be established. A specimen of eight days may resemble one of five or ten days. In some, the proliferation of the tendon is marked, while in others the proliferation is very slight. In some, the graft remains almost entirely viable, while in others it becomes almost entirely necrotic. Far from being a discouraging factor, this varied nature of the findings only serve to accentuate the various parts of the healing process. Thus when the intervening tissues are poorly organized, the proliferative changes in the sheath are brought into the foreground.

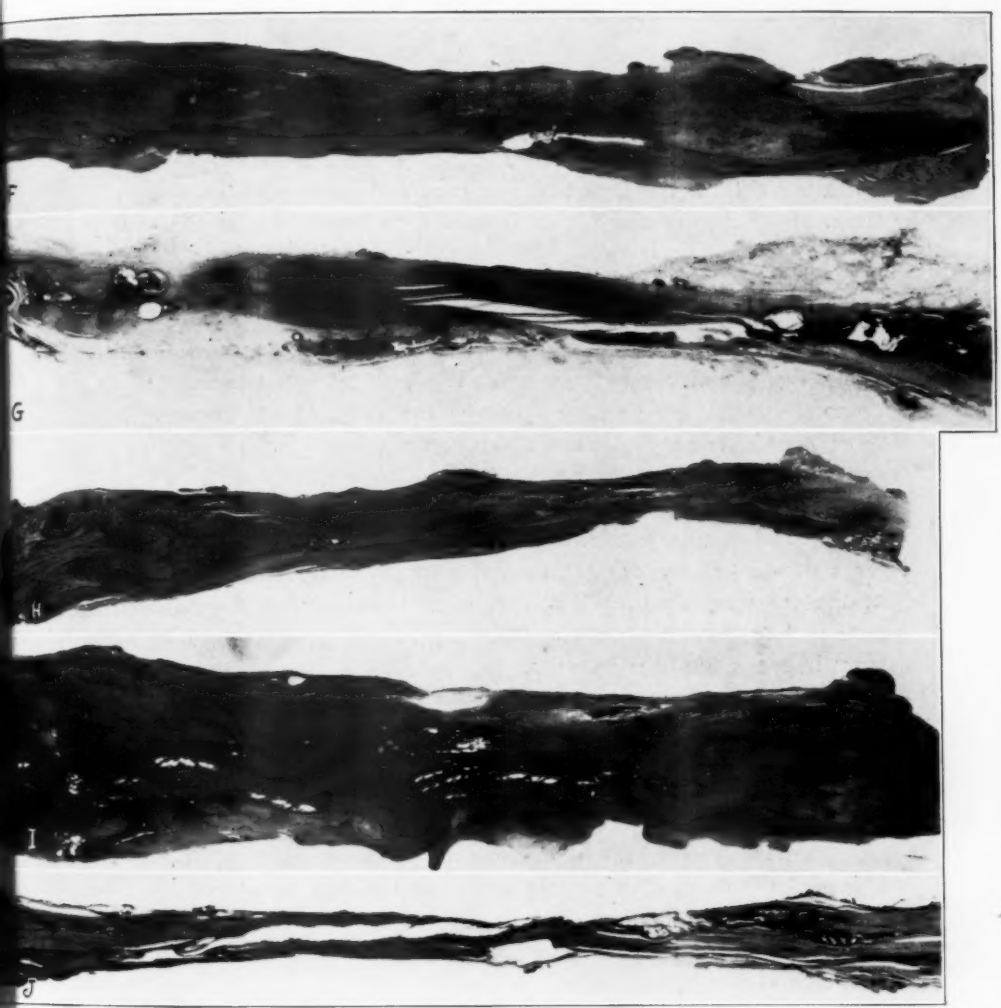
The graft may or may not be living during this eight to ten day period. There may be large areas of necrosis throughout (fig. 12 *A, B* and *C*), frequently infiltrated with leukocytes and certainly taking no part in the healing process. However, in other specimens, large areas of the graft are alive (fig. 12 *D*) and show evidence of proliferation. No very beautiful examples of tendon proliferation are found in these particular specimens, but this is apparently due to chance, since in the next group to be described, good proliferating graft can be seen.

Twelfth to Fourteenth Day.—In specimens removed from the twelfth to the fourteenth day, the proliferative changes seen in the stumps, especially in the proximal stump, have progressed. Throughout the stumps are seen a marked increase in tendon nuclei, an increase in number of the intratendinous blood vessels and of the cells of the endotenonium. The stumps, as a whole, are becoming more nuclear (fig. 13 *A* and *C*), and the longitudinal marking due to the intratendinous vessels is much more in evidence. From the ends of the stumps (figs. 13 *B* and 14 *A* and *B*), the proliferating tenoblasts push



Figs. 25 and 26.—Series of microscopic sections arranged in order of age; at the left, the graft in the center and the distal stump at the right. For description ten days; *C*, T 23, twelve days; *D*, T 22, fourteen days; *E*, T 2 R, fourteen days; *I*, T 13, twenty-five days; *J*, T 11, one hundred days.

outward for a considerable distance into the intervening tissues, and in places (fig. 14 *B*) where the gap between the stump and graft is not great, there is union between the tendon tissues by means of actual tenoblasts. Where the gap is greater (figs. 13 *B* and 14 *A*), the cords of proliferating tendon cells with their rather delicate stroma and large oval nuclei can be followed for long distances into the intervening



reduced from a magnification of × 2½. In all specimens the proximal stump is
tion of specimens refer to protocols of experiments. *A*, T 24, seven days; *B*, T 17,
F, T 10, nineteen days; *G*, T 18, twenty-one days; *H*, T 1 L, twenty-two days;

tissues. In some instances (fig. 15 *B*), it is not possible with moderate magnification to locate the place at which the stump goes over into the intervening tissues.

The sheath tissues about the stumps and graft during this period are still very thick, strong and vascular (figs. 13 *A* and *B*, 15 *A* and 16 *A*). The sheath is still playing a very important rôle in the union,

but not nearly so important a rôle as in earlier specimens. It is much more adult in character, is dense and fibrous and arranged as long bands parallel to the course of the tendon.

The tissue intervening between the stumps and graft is beginning to assume adult character. In some favorable instances in which there has not been too much separation between the tendon ends, this gap has been filled in with a scar the origin of which is from (*a*) the proliferating sheath that dips into the gaps and helps organize them, (*b*) the proliferation of fibroblasts from the endotenonium at the ends of the stumps and graft and (*c*) from the infiltration of tenoblasts from the ends of the tendon. Although, macroscopically, the places at which tendon goes over into intervening tissue is often easily distinguished (fig. 25 of dog T 22 and fig. 26 of dog T 10), the distinction is not easily made under magnification. There is seen a transitional zone from tendon stump to intervening tissue (fig. 15 *B*) through which tenoblastic fibrils may be traced from the stump far into the tissues, or in case apposition is good, clear across the gap from stump to graft (fig. 14 *B*). The intervening tissue (fig. 15 *C*) is becoming arranged in longitudinal rows of cellular fibers; the nuclei are flattening out and are becoming arranged in a direction parallel to the pull of the forming tendon. The numerous blood vessels throughout the tendon scar show a beginning tendency to run in parallel longitudinal rows between the fiber bundles.

The changes noted in the stumps in the twelve to sixteen day specimens are also seen in the graft, though in not quite so advanced a stage (fig. 16). The proximal end of a twelve day graft shows the same budding of tenoblasts (fig. 16 *C*) as was seen in the stumps. In places in which apposition has been good, these bundles may be traced across the gap (fig. 14 *B*) to mingle with the tenoblasts from the stumps. The nuclei throughout the graft are becoming more numerous (fig. 16), oval or round in shape and vesicular. This nuclear increase tends to occur in areas of oval zones or longitudinal strips (fig. 16 *B*), as was noted in the stumps. Along with the nuclear increase, the tendon fibrils tend to lose their wavy course and to form long straight bands of fibers, as seen in figure 16 *A*, in which tendon fibers of the graft along the lower edge of the section are still wavy, while those in the upper part were flattened.

A specimen removed at fourteen days (from dog T 29) and tested rather crudely for strength broke with 11½ pounds pull through the proximal intervening tissue, which, while fairly well organized, was not yet capable of function. The sheath union is still the stronger, though its importance is not so great as in the earlier specimens.

Third Week.—During the third week, the organizing tendon is beginning to show a certain uniformity of structure (fig. 17). It is still possible to distinguish the stumps, the graft and the intervening

tissues, but they are behaving as a whole, and are becoming organized into dense fibrous-like strands. The stumps show resting tendon tissue in but a few areas and these at a distance from the suture line. Most of the stump (fig. 17 *A* and *D*) is made up of closely packed fibers arranged in longitudinal strands with longitudinally placed blood vessels running between them. The nuclei in these strands are very numerous and are flattening out; many are quite flattened (fig. 18), though the oval forms noted in the earlier specimens have not entirely disappeared. The intervening tissues (fig. 17 *C*) and the graft (fig. 17 *B*) are also made up of solidly packed fibers. In the region of the graft, one can occasionally make out small stretches of deeply eosin-stained adult tendon, but the majority has been converted into the same type of cellular tissue as was noted in the stumps. The sheath is no longer the important uniting structure that it had been previously. It is still thickened, but is beginning to loosen up and is more easily separated from the tendon. It is assuming the important function of serving as gliding tissue for the new tendon.

Fourth to Fifth Week.—During the fourth and fifth weeks, the tendon attains great strength, owing to the further development of the tissues coming from the stumps and graft. The stumps and area between them become narrower and more condensed. The newly formed tendon (fig. 19 *C*) is covered over by loose sheets of new sheath tissue, which allow it to glide freely. Tendons at this stage will sustain a pull of from 36 to 40 pounds before rupturing. In two instances (figs. 19 *B* and *C* of dog T 31 and *C* and *D* of Dog T 27), the break occurred at the distal suture line; in one instance (fig. 19 *A* of dog T 28), the rupture took place at the proximal suture line with a pull of slightly over 40 pounds.

The microscopic changes during the fourth and fifth weeks (fig. 20) are a progression of those observed in the third week. The tissue is becoming more and more compact and is taking on more and more uniformity in structure throughout the whole reorganizing tendon. It is considerably more nuclear than adult tendon, but is not ordinary scar tissue. The stumps (figs. 20 *A* and 21 *A* and *B*) are not so thick and nodular as in earlier specimens. They are made up of parallel rows of dense cellular bands between which run longitudinally arranged blood vessels more numerous than in normal tendon. The nuclei are mainly flattened and arranged in rows parallel to the course of the fibers. Here and there one still sees accumulations of round cells about the vessels (fig. 20 *A* and *C*) or about bits of silk. Even in the parts of the stumps in which the suture has led to great disruption of tendon fibers, the tissues about the disrupted areas are well organized, and in the specimen illustrated (fig. 21 B), the stumps withstood a pull of 35 pounds before rupture took place through another part of the new tendon.

A comparison of tissue taken from the region of the graft and from the tissues that unite graft and stumps (fig. 21 *B* and *C*) show that the whole stretch is made up histologically about the same as the stump, in fact, selected places from these different areas (fig. 20) are practically indistinguishable.

One Hundred Days.—A single dog was allowed to live one hundred days before being killed (fig. 22). The dog had never worn a cast, but had been allowed free full use of the leg immediately after the operation. He had excellent functional use of the leg (fig. 22). In this specimen, we have the further progression of the condensation noted in the tendon removed four to five weeks after operation. The silk through the central parts (fig. 26) was pulled out during sectioning, leaving long defects in the new tendon. It is not possible, microscopically, to determine the limits of stumps or graft. The stumps can be distinguished because they are somewhat wider than the tissue between them, but on microscopic examination (fig. 23 *A* and *B* and fig. 24 *A*), it is seen that they and the thinner tissues between them (fig. 24 *B*) have the same histologic characteristics. The tissues are assuming more and more the appearance of normal tendon, though they can still be easily distinguished from it. The fibers are flattened out into long rows parallel to the line of pull, and the nuclei, much reduced in number in comparison to earlier specimens, are flattened and rod-like and also arranged in parallel rows.

RÉSUMÉ OF HEALING PROCESS OF TENDON GRAFTS

In brief résumé, the process of healing of a tendon graft may be divided into two phases. During the first phase, which may be assigned to the first two weeks, the union between graft and stumps is effected by proliferation of the respective sheaths or peritendinous tissues. This phase represents the period during which the tendon is becoming more vascularized and is itself beginning to proliferate. The second overlaps the first and is the phase of tenoblastic proliferation. It begins about the fourth or fifth day after operation, i. e., at the time the first tendon mitoses are apparent. The effectiveness of the union due to the tendon participation depends on the amount of separation between the tendon and graft. Usually by the end of the second week the process is well under way and small defects are already bridged across by tenoblasts. From the second week on, the second phase becomes the most important, so that the new tendon is formed essentially from the organization of a scar that lies between the ends of the graft and stumps and in the formation of which the tenoblasts themselves play the most important part. As the importance of the sheath as a uniting structure diminishes, it begins to take up the important function of serving as gliding tissue. During the fourth and fifth

postoperative weeks, the sheath becomes progressively more easily separated from the organizing tendon, and with successful union there results a well organized tendon with a paratendon arrangement about it. A new synovial sheath has not been observed to form during the period of these experiments.

COMMENT ON RESULTS OF EXPERIMENTAL WORK

The process of healing of tendon wounds is seen to be dependent on a number of different factors that are mutually interactive and that are all essential to a proper reestablishment of functional continuity. It is believed that in the surgical repair of injured tendons a knowledge of the histologic process of repair should result in an improvement of results in this difficult field. It is believed also that with this knowledge as a background, further experimental work can be done with profit.

THE IMPORTANCE OF THE SHEATH AND PERITENDINOUS TISSUES

The connective tissues surrounding the tendon, with the exception of the dense osteofibrous tunnels, are of the greatest importance in the repair of a tendon wound. They have the most intimate relation to the tendon, convey blood vessels and lymphatics to it, and permit easy gliding of the tendon. In the case of such tendons as the extensors on the dorsum of the hand or foot, as the achilles tendon and a few other paratenon covered tendons, the sheath tissues can provide for spontaneous repair, albeit often in a lengthened condition. Even where the sheath tissues are scanty, as, for example, in the synovial covered tendons, they are also important, but, depending on their amount, are less efficient than paratenon. For example, in the wrist the tendons are covered by a synovial sheath, and are provided with a rather large and continuous mesotenon that brings blood vessels and lymphatics to the tendons. Because of the number of tendons enclosed in one synovial layer, there is a good deal of connective tissue associated with the mesotenon and lying between the various reflections of the synovial sheet. While spontaneous repair at the wrist does not take place, operative repair, if correctly done, has a fairly good prognosis. The flexor tendons throughout their course on the fingers, however, have very scanty synovial sheaths. The visceral layer of the synovial sheath lies directly on the surface of the tendon, with very little, if any, connective tissue below it, and the parietal layer is likewise closely applied to the inner surface of the osteofibrous canal. The mesotenons of these tendons are reduced to tiny bridges, the vincula, which carry tiny blood vessels, possess little connective tissue and tear away from the tendon if any great pull is put on them. In tendons of this type, it is obvious that the sheath would be of little value in repair, and that here other methods of suture or surgical repair would have to be applied than in the case of tendons on the dorsum of the hand or in

the wrist. In the comment on tendon repair that follows, the tendons on the volar surface of the fingers, enclosed in synovial sheaths with osteofibrous tunnels, are not included.

As soon as a defect in a tendon results, the tendon ends retract a variable distance, and the sheath tissues fall at once into the resulting gap. If the defect has been sutured, a similar though usually smaller gap frequently occurs, and we have found it always to occur experimentally. Under favorable circumstances, the sheath begins to proliferate shortly after the injury, and by the end of four or five days has produced a bridge of fibroblastic material which encloses both stumps and tends to prevent or at least to minimize further separation. This first callus, like callus on a fractured bone, produces a nodular swelling at the site of injury. During the next two weeks this fibrous bridge forms the more important and at times, if the gap is too great, the only union between the stumps. If the gap is not too great, the tendon proliferation will be able to bridge it successfully in two or three weeks under the protective splinting of the sheath. If too great a gap exists, a union of a sort takes place which is mainly connective tissue and is liable to further stretching.

After the sheath serves its initial function of uniting the stumps, the outer layers loosen up and again take over the function of serving as gliding tissue for the tendon.

It is important, then, in suture of a divided tendon that the sheath tissues be as carefully handled and preserved as the tendon itself. The greatest care should be exercised to avoid stripping this tissue from the tendon. Transverse division of this tissue should be avoided, or, if the sheath is already divided transversely, it should be repaired. If possible, sheath tissues of one stump should be united with as little trauma as possible to similar tissues of the other stump. In operating on enclosed tendons in the synovial sheath, the mesotenon should not be disturbed, but should be left attached to the tendon even though suture is more difficult.

In the case of tendon graft the sheath tissues are seen to take an important part in healing, comparable to that in repair by suture. The first tissues of a graft to show signs of proliferation and to effect union are the connective tissues surrounding it. As in the case of suture, the gaps at either end of the graft are first bridged across by connective tissue resulting from the proliferation of the sheaths about the stumps and graft. This union serves to splint the graft in place until the tendons can directly unite by tendon cell proliferation.

Therefore, in performing a tendon graft, the graft should be left surrounded by its own, carefully handled and preserved, peritendinous tissues. These tissues should be united to similar tissues about the stumps.

THE TENDON

We believe that these studies have shown that the tendon itself takes an important part in healing, but that, because of its scanty blood supply and the very nature of its tissue, it begins its proliferation late and that it progresses more slowly than ordinary connective tissue. This tardiness of tendon response is compensated, however, by the early response of the sheath.

To take advantage of tendon proliferation, one must carefully avoid traumatizing the tendon, and especially must one avoid injury to the ends of the tendon that one wishes to bring together. These studies have shown that the tendon ends start to proliferate about the fourth or fifth day after suture and to send out bands of cells and fibrils into the gap tissue beyond. If the tendon is injured, or if it is stripped of blood supply, necrosis is likely to occur and delay the process.

This consideration of avoidance of injury of the end of the tendon leads one to doubt the wisdom of sutures that pass through the end of a tendon and lead to the disruption of its fibers. Certainly the wisdom of placing knots between the ends of united tendons is doubtful. Microscopic sections show that these cause a very definite barrier between the tendon ends and prevent, for a considerable time, the ingrowth of tendon fibers into the gap.

A tendon suture, it seems to us, should combine two properties, first that of preventing or minimizing retraction and that of obtaining a good end-to-end apposition. The first of the requisites may be met by the use of a tension suture that has a secure hold on the tendon and will not split through it. The points of attachment of the suture to the tendon should be 1 cm. or more from the end of the stump so as to leave this untraumatized. It should be tied so that the knot does not lie between the tendon ends. The second of these properties is met by an appositional suture, which should be of very fine material and threaded on very fine needles. It should be passed through the tendon end in such a manner as to traumatize it as little as possible. It may be placed through sheath tissues, as is done in suturing nerves, or it may pass through the very periphery of the tendon. A single fine suture passed first through one stump and then through the other and tied outside may be enough to maintain apposition. Experimental work now in progress with this type of suture has given promising results, as have also several clinical cases. The presence of the silk on the outside of the tendon does not apparently interfere with function, while the absence of a knot between the ends is an advantage.

Retraction.—Retraction has always occurred despite careful and satisfactory suture and efficient splinting. Whether this is true in surgical intervention on human beings we cannot say, but we may reasonably assume that it is. Since it is necessary that the gap be

bridged across by tendon, it is evident that the wider the gap, the greater the distance the tendon fibrils and cells must penetrate and the greater chance there is for scar tissue to interfere. It may be wise in performing end-to-end suture of tendon in instances in which tension is considerable to put in a small segment of tendon graft. It has been shown that under favorable circumstances the graft remains viable and proliferates and unites with either stump at the ends of the defect. In this manner a tendon-to-tendon union is more quickly obtained.

Tendon Grafts.—These experiments have shown that tendon with its surrounding connective tissue maintains its vitality when transplanted as a free graft. The sheath very soon fuses with the sheath tissues of the two stumps, the tendon itself remains alive and soon proliferates and fuses with the stumps. In this manner actual tendon tissue bridges the defect. Although many surgeons have advocated the use of fascia or other connective tissues for tendon grafts, their position does not seem logical. A fascial tendon or a tendon formed about silk is after all scar tissue, and as such has all the defects of scar tissue—the danger of contracting or of stretching.

SUMMARY

The process of healing of tendon wounds and the manner in which injuries of tendons are repaired following suture or graft have been and still are a matter of considerable controversy. The most controversial question has been the source of the material which forms the tendon callus, and it appears from a study of the literature that investigators have in the main attempted to show that either the tendon itself played the major rôle in healing or that the connective tissues associated with the tendon were the important sources of material. In the present experimental study carried out on the extensor carpi radialis tendon of the dog, an attempt has been made not only to ascertain the source of tendon callus, but to evaluate the parts taken by the various tissues concerned. It is shown by histologic study of healing tendon sutures that union is effected first by proliferation of the sheath tissues. This union serves to reestablish continuity in a few days. After the fourth or fifth day the tendon itself begins to proliferate and to send cells into the callus, and, if the gap is not too great, it may be bridged by tendon cells in about two weeks. After the sheath has served its purpose of splinting the first union, it begins to become more lax and areolar and in a successful suture to take on again its original function of serving as gliding tissue. In the experiments with autogenous tendon grafts, a process of healing similar to that of sutured tendons was found to take place. The only variation between the two processes was that the sheath of the graft and the tendon of the graft remained viable and took part in the bridging of the gap between the

separated stumps. From these experiments it would appear that the following practical conclusions can be drawn:

1. In tendon suture the sheath tissues, if any are present, should be as carefully approximated as the tendon, since they afford an early union which functions while the tendon itself is proliferating. 2. Accurate end-to-end apposition of tendon stumps is beneficial to healing. 3. Movements of sutured tendons may be started cautiously by the fifth or sixth day, but no force should be exerted before the third week. 4. Defects in tendons should be filled with a tendon graft plus its sheath tissues and not by fascia, since the tendon graft forms true tendon which will not tend to stretch as would ordinary connective tissue.

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TRAUMATIC SHOCK

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The current theories as to the initiation of traumatic shock have been reviewed so often and so well [1] that it will not be necessary to repeat them. In 1919, Cannon and Bayliss [2] traumatized the thigh muscles of cats and other animals, thus producing a prolonged lowering in the blood pressure, which they ascribed to a toxin originating in the traumatized area. Since that time, the toxic theory of traumatic shock has become widely accepted. The actual experiments reported were few, and the data were scanty. The original theory was based largely on the analogy to shock produced by histamine. Since that time many others have worked on the problem, with the result that there has been practically no positive evidence of toxemia, while there has been considerable direct negative evidence. The argument for toxemia rests largely on the presumptive exclusion of other factors, the chief of which are the nervous system and hemorrhage. The question remains as to whether the nervous system and hemorrhage were completely excluded in the experiments of Cannon and Bayliss. More recent workers, particularly Parsons and Phemister [3] and Blalock with his

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1. Cannon: Traumatic Shock, New York, D. Appleton & Company, 1923. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:959 (June) 1930. Smith, M. I.: Studies on Experimental Shock with Especial Reference to Its Treatment, J. Pharmacol. & Exper. Therap. **32**:465 (April) 1928.

2. Reports of Shock Committee of the British Medical Research Committee, London, His Majesty's Stationery Office, 1919, nos. 25, 26 and 27.

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associates,[4] have offered proof that hemorrhage together with local fluid loss in the traumatized area can explain all the phenomena. However, even in their experiments it is questionable whether the nervous system had been completely excluded. There are other objections which will be offered later. The two factors, nervous system and hemorrhage, will be discussed separately.

Since the majority of the experiments were on trauma as applied to the muscles of a posterior extremity, the nervous system was excluded by so-called denervating the limb or cutting the spinal cord in the lower dorsal region. In many instances it is not stated specifically what is meant by a denervated limb. For example, the complete peripheral denervation of the thigh in a cat, so that no possible sensory impulses can travel to the central nervous system, involves the severance of at least eight nerves:[5] the femoral, sciatic, obturator, genitofemoral, lateral femoral cutaneous, posterior femoral cutaneous, superior gluteal and inferior gluteal. In addition, an arterial sympathectomy must be done. This could hardly be accomplished as an acute experiment, since the trauma of the operative procedure alone might cause sufficient shock to lower the blood pressure to a shock level. Even when the spinal cord is cut in the lower dorsal region, impulses could still travel up the sympathetic chain to a level above the point of severance. A spinal section cannot be done as an acute experiment without confusing the cause of the fall of blood pressure. In addition to cutting the cord, there is a sympathetic chain on that side that must be partly removed. Since in most of the previous experiments pretending to exclude nervous impulses either the cord alone or only the femoral and sciatic nerves were cut, we must conclude that while the experiments are suggestive that nervous impulses do not initiate traumatic shock, this has not been proved conclusively.

To exclude hemorrhage as the initiating factor is also very difficult. All trauma is accompanied by hemorrhage, and there are no exact

4. Blalock, Alfred: The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, Arch. Surg. **22**:598 (April) 1931; The Importance of Local Loss of Fluid in the Production of Low Blood Pressure After Burns, ibid. **22**:610 (April) 1931. Beard, J. W., and Blalock, Alfred: The Composition of the Fluid that Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines, and After Burns, ibid. **22**:617 (April) 1931. Johnson, George S., and Blalock, Alfred: A Study of the Effects of the Loss of Whole Blood, of Blood Plasma and of Red Blood Cells, ibid. **22**:628 (April) 1931. Harris, P. N., and Blalock, Alfred: Observations on the Water Content of the Body After Trauma and After Hemorrhage, ibid. **22**:638 (April) 1931. Blalock, Alfred: Trauma to the Intestines, ibid. **22**: 314 (Feb.) 1931.

5. Reighard and Jennings: Anatomy of the Cat, New York, Henry Holt & Company, 1925.

methods for accurately measuring the amount. Cannon and Bayliss weighed both the traumatized and untraumatized limbs in cats and took the difference in weight as representing the loss of blood. They concluded, without reported control bleeding experiments, that the loss was not sufficient to account for the fall in blood pressure. Furthermore, they amputated the limb in the upper region of the thigh, so that it is questionable whether they were entirely above the area of extravasation. Parsons and Phemister, and also Blalock, working with dogs, used many more animals than Cannon and Bayliss but came to opposite conclusions. They stated definitely that the loss of blood being over 40 per cent of the estimated blood volume, it was sufficient to account for the shock. The objection to the latter groups of experiments is that the amount of trauma applied was not constant in the various experiments. Trauma was continued at frequent intervals until the blood pressure fell to the desired level. Obviously one can traumatize an animal enough to cause a fatal hemorrhage. The important point would be to see with how little hemorrhage shock could be produced by trauma, and the period of trauma should be very brief if it is to correspond with clinical phenomena. After determining the loss of blood in traumatized animals, other animals of comparable weight should be bled the same amount in practically the same length of time in order to observe whether the blood pressure curve, clinical symptoms and end-results are the same as those following trauma.

The question of whether the blood is actually concentrated in traumatic shock should be settled more definitely so that it can be determined whether this is a reliable sign in differentiating shock from hemorrhage. The evidence on this point is so conflicting that it is impossible to reach any conclusions. The anesthestic effects and the duration of the experiments are important factors.

The experiments reported here were planned to obviate these objections. The purpose was (1) to establish a control series in which a definite brief trauma, not repeated, would cause a permanent fall in blood pressure with symptoms analogous to those of clinical shock, (2) to exclude the nervous system completely, (3) to measure the amount of blood lost in the traumatized area, (4) to bleed animals of comparable weight the same amount in a brief period and to compare this with the effects of trauma and (5) to determine from hemoglobin estimation of the arterial blood whether there was concentration or not.

CONTROL EXPERIMENTS

Method.—Cats weighing from 2 to 4 Kg. were anesthetized by the intramuscular injection of sodium barbital, 0.3 Gm. per kilogram of body weight. A cannula was inserted in the carotid artery. Trauma was produced by striking the inner aspect of one thigh one hundred and fifty rapid blows with a wooden mallet. This

was always done by the same person so that the strength of the blows was fairly constant. The whole period of trauma was less than five minutes. Blood for hemoglobin determination was drawn from the exposed brachial artery before and at intervals after the trauma.

In previous experiments it was found impossible in dogs to produce constantly a typical picture of shock by traumatizing the muscles for a single brief period. However, in cats weighing less than 4 Kg., one hundred and fifty rapid blows to the thigh with a wooden mallet during the period of about three minutes practically

TABLE 1.—*Results in Control Experiments Following Trauma*

Number	Weight, Kg.	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Relative Hemoglobin, per Cent*	Relative Solids, per Cent
1	2.69	144	56	4 hrs. 5 min.	82	..
2	2.91	116	62	3 hrs. 10 min.	79	..
3	2.75	138	Died	8 min.	..	..
4	2.35	148	Died	15 min.	..	..
5	3.015	150	Died	14 min.	..	..
6	3.085	175	76	4 hrs.	85	..
7	2.015	159	Died	1 hr. 32 min.	73	..
8	2.94	162	50	2 hrs. 30 min.	79	..
9	2.690	144	58	4 hrs. 5 min.	82	..
10	2.7	164	52	3 hrs. 50 min.	81	..
11	2.850	162	Died	2 hrs. 50 min.	63	..
12	2.5	145	80	3 hrs. 30 min.	92	..
13	3.3	160	55	3 hrs.	80	..
14	2.563	152	115	3 hrs. 40 min.	91	..
15	2.47	130	80	3 hrs. 50 min.	86	..
16	2.77	120	63	3 hrs. 5 min.	92	..
17	2.615	152	50	3 hrs. 10 min.	78	..
18	2.0	160	Died	2 hrs. 55 min.	84	85
19	4.0	160	Died	3 hrs. 25 min.	85	..
20	2.8	170	92	1 hr. 45 min.	..	..
21	2.5	170	60	1 hr. 25 min.	76	80
22	3.4	180	120	2 hrs. 20 min.	100	99
23	3.6	140	108	2 hrs. 55 min.	..	..
24	2.2	148	52	3 hrs. 5 min.	90	92
25	1.9	140	78	3 hrs. 25 min.	..	..
26	2.2	150	100	2 hrs. 55 min.	88	90
27	2.7	160	Died	1 hr. 45 min.	..	..
28	2.3	180	80	1 hr. 50 min.	98	98
29	1.9	156	80	2 hrs. 5 min.	..	..
30	3.25	160	Died	2 hrs.	83	82
31	2.5	162	Died	50 min.	75	83
32	3.05	170	114	3 hrs.	93	93
33	2.1	150	82	1 hr. 40 min.	..	..
34	2.6	160	62	2 hrs.	..	..
35	3.5	180	70	1 hr. 25 min.	..	..
36	3.0	130	78	1 hr. 55 min.	96	99
37	1.95	152	38	1 hr. 40 min.	76	74
38	2.6	150	Died	2 hrs. 5 min.	86	88
39	2.45	170	Died	2 hrs. 30 min.	98	..
40	2.94	184	Died	2 hrs. 15 min.	..	..

* First determination of hemoglobin and solids on the blood drawn before trauma is taken as 100 per cent.

always produced a typical blood pressure curve with the clinical picture of shock. Nothing was done to the animals after the trauma except to record the blood pressure every five minutes and to take small samples of blood from the brachial artery for hemoglobin determinations.

Results.—Forty animals were used as controls (tables 1 and 2). Thirteen died in periods varying from eight minutes to three and one-half hours following trauma. The average time from trauma to death was one hour and forty-five minutes. Twenty animals had a blood pressure of 80 mm. of mercury or below at the end of the experiment,

which lasted from one and one-half to four hours after the trauma, with an average of two hours and fifty minutes. Only seven animals had a blood pressure of over 80 mm. in experiments lasting from one hour and forty minutes to three hours and forty minutes. In three of these the blood pressure was below 100.

Blood Pressure: The blood pressure curve following trauma was constant (fig. 1). There was a sharp rapid fall of from 50 to 100 mm. of mercury beginning about the middle of the trauma and more pronounced toward the end. In some instances the fall would continue a few seconds after the trauma. More often, however, it was beginning to rise before the trauma was ended. There was a rapid recovery of about half of the fall within a few minutes and a slower recovery, lasting from fifteen to thirty minutes, to within 20 or 30 mm. of the initial blood pressure. Following this, there was a slow fall to a level of 80 mm.

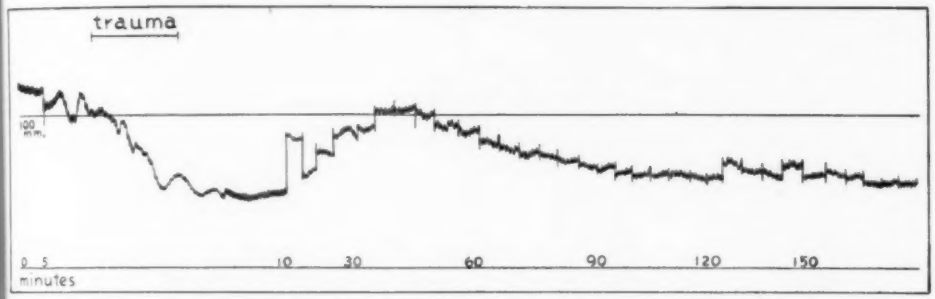

Fig. 1.—Blood pressure curve of a traumatized female cat (weight 3 Kg.) anesthetized with sodium barbital. At *x—x*, the left thigh was struck one hundred and fifty times.

or below in most of the experiments, which continued indefinitely with almost no tendency to recovery. In a few experiments the blood pressure kept falling rapidly until death occurred, with no tendency to recovery following the trauma.

In order to ascertain the effect of the dosage of barbital on the blood pressure curve, seven experiments were done in the manner previously described but with the trauma omitted (table 3). The cats weighed from 2 to 4 Kg., and the duration of the experiments was two and one-half to three and one-half hours. While occasionally there were variations in the blood pressure, the curve did not resemble that following trauma, and at the end of the experiment the blood pressure was about the same as at the beginning.

Pulse and Respiration: There was no characteristic change in the pulse rate except that when the pressure dropped to below 50 mm., the pulse suddenly became very slow, then after the pressure rose the rate

suddenly jumped back to the original speed or higher. As the experiment progressed the pulse rate remained very close to the original rate. Sometimes it was slower and sometimes slightly more rapid.

The respiration became more rapid and irregular during the period of trauma but soon settled down to a rhythm more rapid and shallower than at the beginning.

The foregoing experiments showed that in small cats a single brief interval of trauma applied to the muscles of one of the posterior extremities could constantly produce a condition simulating clinical shock with a constant typical blood pressure curve. This curve consisted of primary shock with recovery, a latent period, and then sec-

TABLE 2.—*Summary of Table 1*

Number of Animals	Died	Blood Pressure Below 80 Mm.	Blood Pressure Above 80 Mm.	Average Hemoglobin Reduction*	Average Solid Reduction†
40	13	20	7	15%	11.4%

* Twenty-eight animals.
† Twelve animals.

TABLE 3.—*Results in Control Experiments Without Trauma*

Number	Weight, Kg.	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin, per Cent of Change
1	2.7	170	120	2 hrs. 40 min.	...
2	1.9	124	120	2 hrs. 45 min.	...
3	...	155	125	2 hrs. 40 min.	...
4	2.46	130	120	3 hrs. 30 min.	−2
5	2.85	160	160	3 hrs. 20 min.	0
6	2.29	130	120	3 hrs. 30 min.	+1
7	2.67	140	134	3 hrs. 30 min.	−3

ondary shock, thus offering the same picture as was developed clinically during the Word War. The remarkable constancy of this blood pressure curve with the four definite divisions, a sharp rapid fall during trauma, rapid partial recovery, maintenace of a level for a brief period and secondary fall, gave a characteristic control curve for comparison in the following experiments.

EXCLUSION OF THE NERVOUS SYSTEM

The complete exclusion of the nervous connections of the limb can be accomplished by (1) cutting all the peripheral nerves, removal of the lumbar sympathetic chain and arterial sympathectomy; (2) cutting the spinal cord in the lower dorsal region in addition to the removal of the lumbar sympathetic chain and arterial sympathectomy, or to be absolutely sure, (3) the combination of cutting the cord, nerve section, lumbar sympathectomy and arterial sympathectomy. Any of the fore-

going procedures involve considerable operative trauma, hardly leaving the animal in a fit condition for an immediate experiment on traumatic shock. Therefore, it was necessary to do the nerve operations in stages as recovery experiments. For the first stage, the peripheral nerves and the sympathetic chain were severed, and a week or ten days later the lower dorsal cord was cut. These operations were done with aseptic precautions under ether anesthesia. From four to seven days following the section of the cord, with the animals in good condition, the shock experiments were done under sodium barbital anesthesia. Eleven animals were used. In four the cord alone was cut, in five the cord was cut, the bilateral lumbar sympathetic chain was removed and the iliac artery was stripped of its sheath, and in three the cord was cut in addition to the nerves, the lumbar sympathetic chain was removed and the iliac artery was stripped.

TABLE 4.—*Results in Nerve Experiments*

No.	Operation	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time
1	Cord cut	142	Died	55 min.
2	Cord cut	130	80	2 hrs. 45 min.
3	Cord cut	140	Died	45 min.
4	Cord cut	110	62	1 hr. 50 min.
5	Cord cut with sympathetic	156	80	2 hrs. 25 min.
6	Cord cut with sympathetic	120	118	2 hrs. 5 min.
7	Cord cut with sympathetic	130	60	2 hrs. 25 min.
8	Cord cut with sympathetic	120	64	1 hr. 25 min.
9	Cord cut with sympathetic	114	Died	1 hr. 15 min.
10	Cord cut, sympathectomy, nerves cut	144	96	1 hr. 45 min.
11	Cord cut, sympathectomy, nerves cut	120	76	1 hr. 40 min.

Results.—The results (table 4) were essentially similar to those in the control experiments. Three animals died in an average of eighty minutes, six had a blood pressure of 80 or below in average time of two hours and five minutes and two had a blood pressure of over 80 in average time of one hour and fifty-five minutes. The conformation of the blood pressure curve (fig. 2) did not differ from that of the controls. We can conclude, therefore, that the nervous system does not play an important rôle in the production of low blood pressure following trauma.

HEMORRHAGE

The problems involved in determining the rôle of hemorrhage following trauma are (1) to develop a relatively accurate method of determining the amount of hemorrhage in the traumatized area; (2) to bleed animals this amount of blood in a comparable length of time and compare the blood pressure curve with that following trauma.

Method.—At the end of the trauma experiments, both posterior extremities, the traumatized and untraumatized, were amputated at the sacro-iliac joint, the

iliac bone thus being included in order to get well above the area of extravasated blood. The muscles and skin of each leg separately were macerated in a grinder and put in a large amount of distilled water and allowed to stand overnight. The water was changed until the tissues were completely bleached. After filtration, a 10 cc. sample of the pooled washing of each leg was treated with 0.1 cc. of concentrated hydrochloric acid and read in a colorimeter against the Newcomer standard for hemoglobin concentration. The standard had been checked for oxygen capacity. Since the total amount of washings were known, this determination gave the total number of milligrams of hemoglobin in each leg. The difference gave the amount of blood lost in milligrams of hemoglobin.

At the beginning of the experiments and just before the end, blood samples were taken from the brachial artery for hemoglobin determination. The first sample gave the number of milligrams of hemoglobin per hundred cubic centimeters of blood. Since the total number of milligrams of hemoglobin lost was known, the number of cubic centimeters of blood lost could be determined.

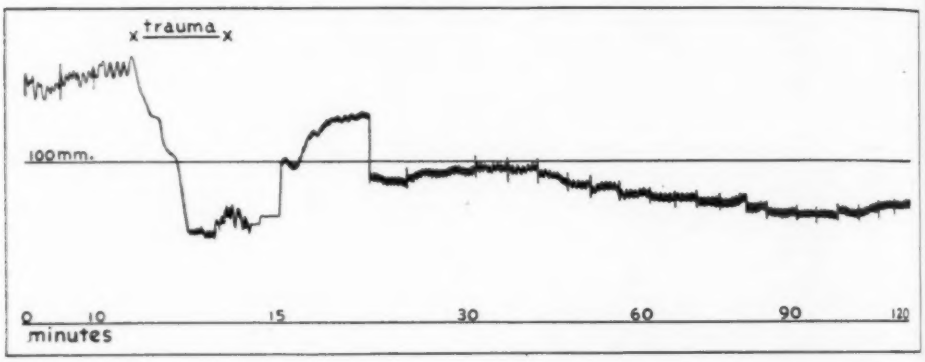

Fig. 2.—Blood pressure curve of a traumatized cat (weight, 2.4 Kg.) anesthetized with sodium barbital. The bilateral lumbar sympathetic chain was removed, and the left iliac arterial sympathectomy done eight days before. The spinal cord was cut in the lower dorsal region two days before. At *x*—*x*, the left thigh was struck one hundred and fifty times.

To check this method, a measured amount of blood was added to macerated muscle and then extracted as previously described. The result (table 5) showed that the error was less than 1 cc. in six experiments, 3 cc. in one, 4 cc. in one and 7.8 cc. in one. The average error was 1.9 cc., which in animals of the weight used would equal about 1 per cent of the blood volume.

To compare the effects of bleeding without trauma, cats of similar weight were bled by needle and syringe rapidly from the exposed femoral artery to the amount equal to the determined loss of blood following trauma. The bleeding time was five minutes or less, thus comparable to the time of trauma and the artery was clamped after the hemorrhage. Rapid bleeding was adopted because it was found that in following trauma, if the vessels were tied immediately, the blood pressure curve was not altered. Therefore, it was the acute bleeding which was the most important factor.

Results.—In comparing the effects of hemorrhage and trauma with equal loss of blood, one is struck by the similarity of the blood pressure

curves (compare figure 3 with figure 4, and figure 5 with figure 6). After hemorrhage there was the same immediate sharp fall with a rapid recovery and a latent period followed by the same slow fall to a low level which was frequently maintained. The general clinical picture

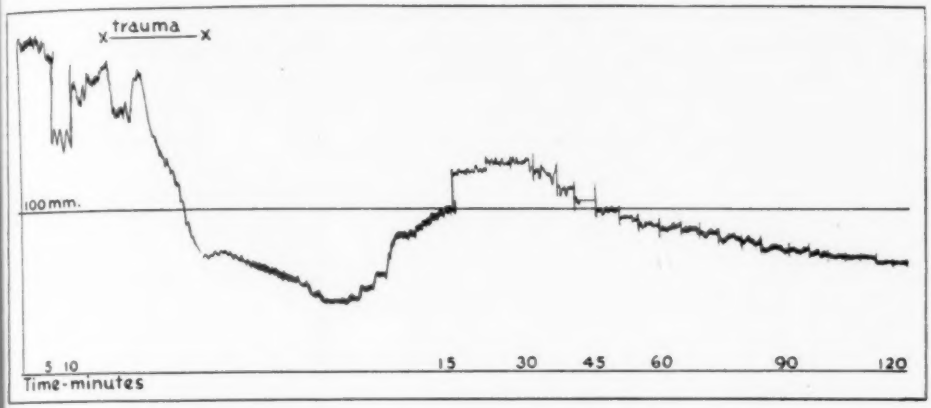

Fig. 3.—Blood pressure curve of a traumatized cat (weight, 2.7 Kg.) anesthetized with sodium barbital. At *x*—*x*, the left thigh was struck one hundred and fifty times. The loss of blood in the traumatized extremity measured 29.5 cc., or 15 per cent of the estimated blood volume.

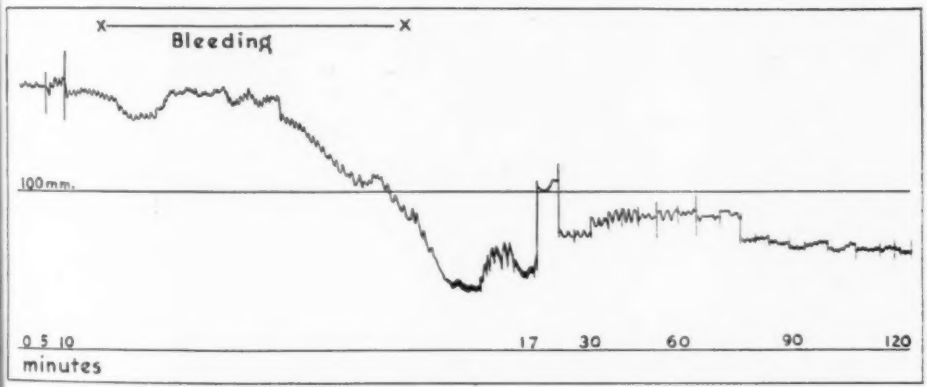

Fig. 4.—Blood pressure curve of a bled cat (weight, 3 Kg.) anesthetized with sodium barbital. At *x*—*x*, 34 cc. of blood, or 15 per cent of estimated blood volume, was taken from the left femoral artery. There was no trauma.

was the same. The pulse and respirations are similar whether the loss of blood was caused by bleeding or by trauma.

However, as the experiments progressed, it was evident that although individual cases of trauma and bleeding with the same loss of blood could be selected which were almost identical, nevertheless, in the whole

series of experiments, the animals traumatized seemed more severely injured than those bled. If we divide the animals into two groups according to the loss of blood, (1) those with a loss of from 20 to 30 per cent of the estimated blood volume and (2) those with a loss of from 10 to 20 per cent of the estimated blood volume, we find that in group 1 (table 6), of eight animals traumatized, four died in intervals of from eight minutes to one hour and thirty minutes, three had a blood pressure of below 80 mm. after an average period of three hours and one had

TABLE 5.—*Blood Estimation by Hemoglobin Method in Control Experiments*

Number	Original Blood, Cc.	Estimated Blood, Cc.
1	18	18.3
2	15	15.0
3	15	15.4
4	20	18.8
5	25	17.2
6	25	26.0
7	53	52.0
8	66	63.0
9	62	61.5
10	60	56.0

TABLE 6.—*Results in Traumatized Animals in Group 1* *

No.	Weight, Kg.	Loss of Blood, Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1),‡ per Cent	Hemoglobin (2),‡ per Cent	Per Cent of Change
28†	2.915	47.0	22	160	Died	1 hr. 30 min.	59	43	—27
29	3.300	53.7	22	160	55	3 hrs.	65	52	—20
30	3.085	46.6	21	175	80	4 hrs.	83	71	—15
31	2.350	35.6	21	135	Died	15 min.			
32†	3.015	46.5	21	150	Died	14 min.			
33	2.750	60.5	30	140	Died	8 min.			
34	2.690	54.8	28	140	55	4 hrs. 5 min.	62	51	—18
35	2.910	55.4	26	115	60	3 hrs. 10 min.	63	50	—21

* In this group the loss of blood is from 1.4 to 2.1 per cent of the body weight, and from 20 to 30 per cent of the blood volume (estimated). The blood volume is estimated as one-fourteenth of the body weight, which is the figure given by Welcker for cats.

† The vessels were ligated immediately after trauma.

‡ Hemoglobin (1) was taken before trauma or hemorrhage, and hemoglobin (2) at the end of the experiment.

a blood pressure of over 80 mm. at the end of four hours. In nine animals bled the same amount (table 7), two died in an average period of two hours and fifty-five minutes, four had a blood pressure below 80 after a period of four hours and two had a blood pressure above 80 at the end of three hours and twenty minutes.

In group 2 in which the loss of blood was smaller, of eight traumatized animals (table 8), two died in two hours and twenty minutes, four had a blood pressure below 80 mm. at the end of three hours and two had a blood pressure of 80 or above in three hours and one half. Of ten animals bled an equal amount (table 9), none died, two had a blood pressure below 80 mm. at the end of three hours and thirty

minutes and eight had a blood pressure above 80 at the end of about three hours.

The similarity of the blood pressure curve in those traumatized and bled seems to establish hemorrhage as the chief factor in this form of traumatic shock. The more serious consequences following trauma (tables 10 and 11) can be explained by the added loss of fluid locally due to inflammatory edema which Blalock has shown to occur. Before dis-

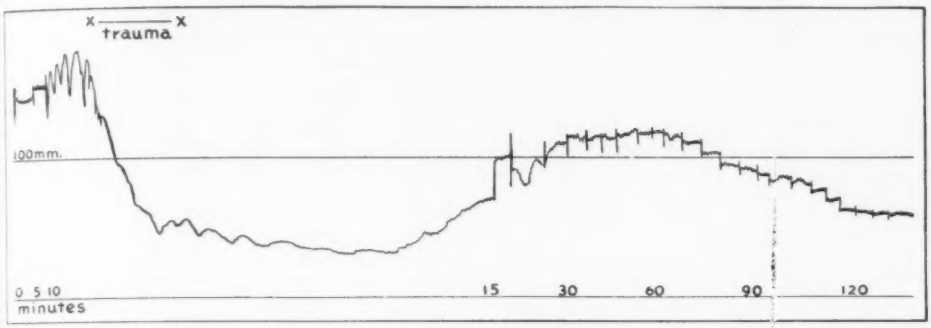

Fig. 5.—Blood pressure curve of a traumatized cat (weight, 2.7 Kg.) anesthetized with sodium barbital. At *x—x*, the left thigh was struck one hundred and fifty times. The loss of blood in the traumatized area measured 54.8 cc., or 29 per cent of the estimated blood volume.

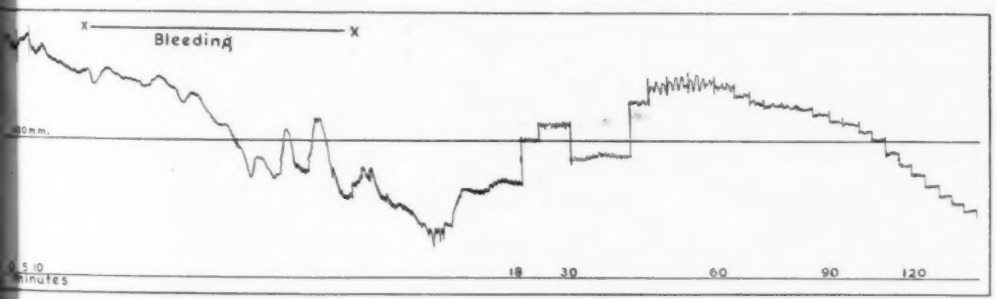

Fig. 6.—Blood pressure curve of a bled cat (weight, 3 Kg.) anesthetized with sodium barbital. At *x—x*, 66 cc. of blood, or 30 per cent of the estimated blood volume was taken from the left femoral artery. There was no trauma.

cussing this point, another factor must be mentioned. As has been stated, in the bled animals the arteries were tied immediately following trauma, while in the traumatized animals the blood vessels remained open. This may have influenced the final results in that, with the vessels open, even though the hemorrhage had stopped spontaneously, as the blood pressure rose, the bleeding might be resumed. However, in eight of the traumatized animals the iliac vessels were tied immediately fol-

lowing trauma. The blood pressure curves and end-results were similar to those experiments in which the vessels were not tied. It seems fair to conclude that it is the sudden acute hemorrhage that is responsible for the typical curve.

TABLE 7.—*Results in Bled Animals in Group 1*

No.	Weight, Kg.	Loss of Blood, Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1), per Cent	Hemoglobin (2), per Cent	Per Cent of Change
19	2.430	41	23	160	100	2 hrs. 45 min.	57	51	—11
20	2.460	40	22	125	Died	3 hrs. 25 min.			
21	2.725	47	23	140	75	4 hrs. 10 min.	61	43	—30
22	2.850	43	21	145	65	3 hrs. 45 min.	64	57	—11
23	2.79	42	21	170	50	3 hrs. 50 min.	56	44	—20
24	3.15	49	21	155	Died	2 hrs. 40 min.	56	44	—20
25	2.45	37	21	110	70	4 hrs. 45 min.	56	51	— 9
26	3.015	66	30	160	Died	2 hrs. 25 min.	77	59	—24
27	2.495	50	29	155	90	3 hrs. 30 min.	80	62	—23

TABLE 8.—*Results in Traumatized Animals in Group 2**

No.	Weight, Kg.	Loss of Blood, Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1), per Cent	Hemoglobin (2), per Cent	Per Cent of Change
11†	2.700	29.0	15	160	60	3 hrs. 40 min.	74	60	—19
12	2.850	35.6	17	165	Died	2 hrs. 30 min.	63	40	—37
13†	2.58	34.0	18	160	50	2 hrs. 30 min.	71	56	—21
14†	2.94	41.7	19	180	Died	2 hrs. 10 min.			
15†	2.77	38.0	19	120	65	3 hrs. 5 min.	66	61	— 8
16†	2.500	23.0	12	145	80	3 hrs. 30 min.	70	64	— 8
17†	2.615	21.0	11	150	50	3 hrs. 10 min.	84	66	—22
18	2.562	23.4	12	150	115	3 hrs. 30 min.	82	75	— 9

* In this group the loss of blood was from 0.7 to 1.4 per cent of body weight, and from 10 to 20 per cent of the blood volume (estimated).
† The vessels were ligated immediately after trauma.

TABLE 9.—*Results in Bled Animals in Group 2*

No.	Weight, Kg.	Loss of Blood, Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Hemoglobin (1), per Cent	Hemoglobin (2), per Cent	Per Cent of Change
1	2.755	32	19	145	110	4 hrs. 5 min.	63	60	— 5
2	3.400	44	18	145	90	3 hrs. 40 min.	65	49	—25
3	2.800	32	16	160	100	4 hrs.	75	67	—11
4	3.060	34	15	160	75	3 hrs. 50 min.	72	62	—14
5	2.975	35	16	140	120	3 hrs.	62	53	—15
6	2.530	27	15	100	110	3 hrs.	51	47	— 8
7	2.85	31	15	150	110	2 hrs. 50 min.	72	65	—10
8	2.35	30	17	150	70	3 hrs. 5 min.	71	62	—13
9	2.72	40	20	130	105	4 hrs.	60	57	— 3
10	2.757	21	10.6	130	105	3 hrs. 15 min.	56	54	— 4

BLOOD AND TOTAL FLUID LOSS

In order to get some evidence as to the local fluid loss in addition to the hemorrhage, five cats were traumatized, the limbs weighed after

amputation at the sacro-iliac joint, and the loss of blood was estimated as in the previous experiments.

Results.—The difference in weight between the traumatized and untraumatized extremities ranged between 50 and 87 Gm., with an average of 68 Gm. This represented hemorrhage plus loss of fluid, which thus averaged about 40 per cent of the estimated blood volume (table 12). The loss of blood as calculated ranged from 36 to 52.7

TABLE 10.—*Summary in Group 2*

	Number of Animals	Died	Final Blood Pressure Above 80 Mm.	Final Blood Pressure Below 80 Mm.	Average Hemoglobin Reduction, per Cent
Hemorrhage	10	0	8	2	10.8
Trauma	8	2	2	4	14.5

TABLE 11.—*Summary in Group 1*

	Number of Animals	Died	Final Blood Pressure Above 80 Mm.	Final Blood Pressure Below 80 Mm.	Average Hemoglobin Reduction, per Cent
Hemorrhage	9	3	2	4	17.3
Trauma	8	4	0	4	18.5

TABLE 12.—*Blood and Total Fluid Loss in Traumatized Animals*

Number	Weight, Kg.	Loss of Blood (Estimated), Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)	Difference in Weight of Traumatized and Untraumatized Limbs, Gm.	Total Loss of Fluid, per Cent of Blood Volume (Estimated)	Loss of Fluid Exclusive of Blood, per Cent of Blood Volume (Estimated)
1	2.940	40.5	19.0	50	23.6	4.6
2	2.135	36.1	23.0	54	35.0	12.0
3	2.310	38.2	23.1	73	44.0	20.9
4	2.385	48.1	28.0	87	51.0	23.0
5	2.430	52.7	27.0	78	45.0	18.0

cc., averaging 43 cc., or 23 per cent of the estimated blood volume. The difference between total fluid and loss of blood averaged 17 per cent of the blood volume. Therefore, local inflammatory edema caused an average loss of fluid of 17 per cent of the blood volume, a loss only 6 per cent less than the loss of blood. Even though the weight method of estimating loss of fluid is crude and inaccurate, yet the difference between loss of blood and gain in weight in the traumatized limb is so marked that it must represent a definite loss of fluid. This loss could account for the more severe effect in loss of blood from trauma than in bleeding from a vessel without trauma.

LIGATION OF VESSELS

To show further the influence of hemorrhage on the blood pressure curve following trauma, experiments were done in which the left iliac artery and vein were ligated just before traumatizing the left thigh. Thirteen cats were used in this group.

Results.—There was no sharp drop in blood pressure during trauma in marked contrast to the control trauma experiments in which the vessels were not ligated (compare figure 7 and figure 1). However, in most of the experiments, after a latent period there was a slow moderate drop in blood pressure with almost complete recovery (table 13). This type of curve was occasionally observed in the control barbital experiments. Even though the chief vessels to the traumatized area were ligated, there was yet a moderate amount of hemorrhage and loss

TABLE 13.—*Results of Vessel Ligation in Traumatized Animals*

Number	Weight, Kg.	Initial Blood Pressure, Mm.	Final Blood Pressure, Mm.	Time	Loss of Blood, Cc.	Loss of Blood, per Cent of Blood Volume (Estimated)
1	3.21	143	145	3 hrs. 35 min.	15.0	6.1
2	3.00	180	150	3 hrs. 40 min.	7.9	3.6
3	2.7	132	94	3 hrs. 30 min.	11.5	6.0
4	2.88	160	130	3 hrs. 25 min.	9.4	4.5
5	3.5	140	155	2 hrs. 55 min.		
6	3.0	180	155	1 hr. 40 min.		
7	2.4	130	125	1 hr. 25 min.		
8	3.4	168	118	2 hrs. 25 min.		
9	2.3	160	120	2 hrs. 50 min.		
10	2.4	150	130	1 hr. 45 min.		
11	2.1	160	128	1 hr. 50 min.		
12	2.6	162	140	1 hr. 55 min.		
13	3.1	160	130	2 hrs. 5 min.		

of fluid. This loss of blood was measured in a few of the experiments and amounted to from 3 to 6 per cent of the estimated blood volume. Thus the slight effect of trauma on the blood pressure with the vessels ligated seems consistent with a small amount of hemorrhage.

BLOOD CONCENTRATION

As the tables show, in both the bled and the traumatized animals, the hemoglobin concentration of the arterial blood was reduced. There was no evidence of blood concentration. The average reduction was 14.5 per cent in traumatized animals with a loss of blood of from 10 to 20 per cent of the blood volume, and 10.8 per cent in the animals bled this amount. When traumatized animals lost from 20 to 30 per cent in the blood volume, the hemoglobin reduction was 18.5 per cent, while in the animals bled this amount it was 17.3 per cent. This seems to furnish further evidence of the importance of hemorrhage as the chief factor in traumatic shock. It shows that in experiments done

under these conditions trauma is not followed by blood concentration. To check this point further in many of the controls both the hemoglobin and the total solids of the arterial blood were estimated (tables 1 and 2). The average reduction in hemoglobin for twenty-eight experiments was 15 per cent, while the average reduction in total solids for twelve experiments was 11.4 per cent. There were no experiments in which the blood showed concentration.

It is possible that the blood concentration found by other observers could have been due in some instances to the long duration of the experiments with resultant dehydration, and in others to the use of ether anesthesia. In our experience, ether anesthesia in dogs always gave rise to a concentration of blood of 10 to 15 per cent as estimated by hemoglobin determinations and occasionally it was as high as 40 per

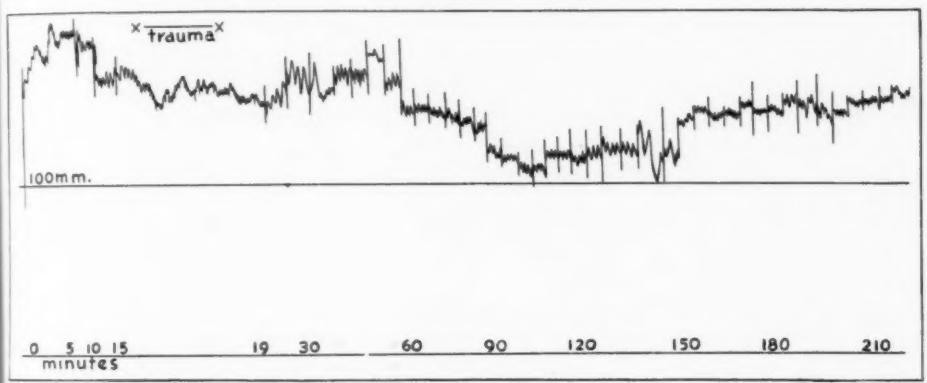

Fig. 7.—Blood pressure curve of a traumatized cat (weight, 3 Kg.) anesthetized with sodium barbital. The left iliac artery and vein were ligated before trauma. At *x—x*, the left thigh was struck one hundred and fifty times. The loss of blood was 3.6 per cent of the blood volume.

cent. In a series of experiments on dogs done under ether anesthesia, out of a hundred dogs, ten small animals either died or had a marked fall in blood pressure quickly, that is, within one-half hour after the anesthetic was started. All of these animals showed a blood concentration of over 25 per cent. This may explain the so-called shock seen so frequently in laboratory animals soon after an inhalation anesthetic is started.

SUMMARY

Cats weighing from 2 to 4 Kg. could be constantly shocked by traumatizing one posterior extremity with one hundred and fifty rapid blows of a wooden mallet. In a control series of forty animals, this brief unrepeated trauma was followed by a typical blood pressure curve con-

sisting of a rapid fall in pressure during trauma, a rapid partial recovery, a level latent period, and then a slow fall into secondary shock. With this large series as a control, experiments were conducted to exclude all the nervous connections of the extremity to be traumatized. In order to accomplish this, recovery experiments were done in stages, cutting the cord, the peripheral nerves and the sympathetic chain. These completely denervated limbs responded to trauma like the controls.

The loss of blood in the traumatized limb was measured, and then other animals of comparable weight were rapidly bled these amounts. Rapid hemorrhage produced blood pressure curves similar in contour to those produced by trauma; however, with an equal loss of blood the end-results were more severe following trauma. Further experiments showed that following trauma in addition to the loss of blood there was a considerable local loss of fluid due to edema. Therefore, the added loss of fluid could account for the more severe symptoms following trauma. This confirms the findings of Blalock.

Measurements of the hemoglobin concentration in the arterial blood checked frequently by the estimation of total solids never showed any concentration following the drop in blood pressure but always a rather marked dilution. This dilution was similar to that following acute hemorrhage.

The shock following trauma can be explained on the basis of hemorrhage and local fluid loss.

PERITONITIS

II. SYNERGISM OF BACTERIA COMMONLY FOUND IN PERITONEAL EXUDATES

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In a previous paper, Meleney, Harvey and Jern presented the bacteriologic findings in a series of 106 cases of peritonitis.[1] They tried to correlate these findings with the clinical course. One of the most significant points brought out in that study seemed to be the fact that when two or more different species of intestinal organisms were present, the clinical course of the illness was much more serious than when a single species was present. This suggested the advisability of studying the synergistic or antagonistic effect of the organisms commonly found in peritonitis secondary to lesions of the intestine.

It has long been known that the intestinal tract habitually contains a number of different bacterial species that are constantly present from the time of early infancy until death. From time to time other organisms may gain a temporary foothold, but they generally come and go and leave the field to those that find the environment continually favorable to their growth. The different species survive in the presence of one another, and it seems reasonable to suppose that they have either an indifferent or a favorable effect on one another's presence. These intestinal bacterial species may be said to be living in a state of symbiosis. This term, taken literally, simply means the coexistence of two or more different species of organisms, but generally the term has a significance of mutual benefit. Some symbionts will not grow if separated from one another. Such a relationship is called an obligatory symbiosis. Others will grow better when together, but will grow to a limited degree if

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separated. Such a relationship is called a facultative symbiosis. On the negative side there are antagonisms in which certain species living in the same place inhibit one another. Then one or the other, or both, may be destroyed. Symbiosis may relate to more than two species living together. In the intestinal tract of man and of animals such is the case, and the relationship of the several species to the common host is not clearly understood. Some think that they are beneficial to the host, others think that they are detrimental, while others believe that the host is indifferent to their presence. When intestinal organisms invade the tissues of the host and give symptoms of disease, it is evident that, while they may be in symbiosis with one another, they are antagonistic to the host, and the host to them.

The term synergism is used when the symbionts are able to perform some function together that they cannot perform by themselves, or in which a function of one is greatly increased by the presence of the other.

HISTORICAL DATA

Symbiosis has been studied extensively by zoologists and botanists, but it has not been given the attention it should receive from the medical sciences. There is fossil evidence that symbiosis is a very ancient phenomenon of nature, and many believe that it is the most potent factor in the origin of species.[2]

One of the best examples of symbiotic existence is the lichen, which is formed by the intimate association of a fungus and an alga, and they are apparently in obligatory symbiosis. Fungi also grow around and in the roots of certain plants and trees, and this association is favorable for the growth of both of these species. Certain nitrifying bacteria that occur in the soil enter the root hairs of leguminous plants and supply the roots with nitrates, accepting in return carbohydrates for their own nourishment.[3]

Bacterial mixtures play an extremely important function in the disintegration of animal bodies, and this forms an important link in the cycle of life.

Symbiosis of bacteria has been observed in the laboratory for a long time, although since the time of Koch efforts have been made to obtain pure cultures and to study the biologic and cultural characteristics of the pure cultures, rather than to study the interaction or cooperative action of mixed cultures. Most of the observations that have been made with respect to bacterial synergism have been made by chance and have had no clinical importance, although they have frequently led to technical procedures of considerable commercial importance.[4] Most frequently, observations of the synergism of bacteria have been made with respect to the fermentation of carbohydrates and the digestion of proteins. A number of authors have shown that two or three different species of bacteria working together are able to perform a function that none of the single species can perform alone. In such circumstances it has been thought that one organism initiates the process

2. Rheinheimer, H.: Symbiosis and Evolution, J. Ment. Sc. **69**:339, 1923.

3. Hastings, S.: Team-Work in Nature, Lancet **2**:774 (Oct. 6) 1923.

4. Sherman, J. M., and Shaw, R. H.: Associative Bacterial Action in the Propionic Acid Fermentation, J. Gen. Physiol. **3**:657, 1920. Speakman, H. B., and Phillips, J. F.: A Study of a Bacterial Association: I. The Biochemistry of the Production of Lactic Acid, J. Bact. **9**:183, 1924.

and the other finishes it, but in some instances, apparently, the organisms have to grow intimately with one another, and the synergistic effect is due to some interaction between the species.[5] Only a very limited number of observations have been reported with regard to the synergistic action of bacteria in disease processes. Castellani[6] listed three disease entities that he believed were due to synergistic action. Trichomycosis alba, trichomycosis rubra and stomatitis cryptococcus bacillaris are all diseases in which two organisms are constantly present, and both of them are necessary for the development of the disease. Vincent's angina is also considered to be due to two different species of organisms, a fusobacterium and a spirillum. Knorr[7] has presented evidence favoring the theory that the streptococcus of the mouth is a necessary accompaniment of these other organisms in the production of the disease. Liermann[8] made some interesting studies of bacterial mixtures in certain putrefactive processes and concluded that they were due to the synergistic action of several species, rather than to a single species. Bienstock[9] in his study of putrefactive organisms, observed that the association of anaerobes with aerobes was necessary for complete putrefaction. Kammerer[10] found that certain bacterial mixtures were essential for the production of hematoporphyrin from hemoglobin, and when he found hematoporphyrin in the fluid of lung abscesses he concluded that this action and possibly the lesion itself were due to a synergistic bacterial action. A very striking example of bacterial synergism was recently observed by one of us (Dr. Meleney) when two organisms that were recovered from a case of chronic empyema were studied. In this instance, the combined action of the organisms produced hemolysis on blood agar plates, when the colonies approximated one another.[11]

In 1926, Dr. Brewer took care of a patient in whom progressive gangrene of the abdominal wall developed following drainage of an appendical abscess. After conservative methods of treatment, the lesion was completely excised. In the periphery of the lesion, cultures yielded a pure micro-aerophilic streptococcus evidently of intestinal origin, while in the gangrenous zone this organism was combined with Staphylococcus aureus. When these organisms were injected into animals in pure culture, no lesion was obtained, but when they were combined they resulted in a violent infection with gangrene, indicating that they had some adjuvant

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5. Holman, W. L., and Meekison, D. W.: Gas Production by Bacterial Synergism, J. Infect. Dis. **39**:145, 1926. Castellani, A.: Fermentation Phenomenon When Different Species of Microorganisms Are in Close Association, Proc. Soc. Exper. Biol. & Med. **23**:481, 1926. Sears, H. J., and Putman, J. J.: Gas Production by Bacteria in Symbiosis, J. Infect. Dis. **32**:270, 1923.

6. Castellani, A.: Importance of Symbiosis or Close Association of Different Species of Organisms in the Production of Biochemical Phenomena and in the Causation of Certain Diseases and Certain Symptoms of Disease, J. A. M. A. **87**:15 (July 3) 1926; J. Trop. Med. **29**:217, 1926.

7. Knorr, M.: Ueber die fusospirillare Symbiose, die Gattung Fusobacterium und Spirillum sputigenum, Centralbl. f. Bakt. **87**:336, 1922.

8. Liermann, W.: Bakteriologische Untersuchungen über putride Intoxication, Centralbl. f. Bakt. **8**:364, 1890.

9. Bienstock: Untersuchungen über die Aetiologie der Eiweissfaulnis, Arch. f. Hyg. **36**:335, 1899.

10. Kammerer, H.: Beiträge zur Bedeutung des bakteriellen Synergismus für die Biologie, Klin. Wchnschr. **3**:725, 1924.

11. Meleney, F. L.: Aerobic and Anaerobic Examples of Hemolytic Bacterial Synergism, Proc. Soc. Exper. Biol. & Med. **24**:205, 1928.

action on one another and that the lesion was due to a synergism of these two species.[12] Recently a similar case yielded identical organisms, and experimental inoculation produced identical results, so that there seems to be very strong evidence in favor of the theory that this lesion is a disease due to the symbiosis and synergism of two bacterial species.[13]

In a recent study of organisms present in raw catgut (representing, of course, intestinal organisms of sheep, which were able to survive the drying process and the passage of time), Meleney and Chatfield found two specimens that yielded a combination of organisms which, when injected into laboratory animals, produced death, while these same organisms in pure culture failed to do so. In two other specimens the combination of organisms produced a skin necrosis that the pure cultures could not produce. Later on, while studying specimens of improperly sterilized catgut, they found two specimens that yielded a mixture of organisms that had a very prompt lethal effect on laboratory animals when injected together, but which in pure culture were entirely nonpathogenic.[14]

It has been known for a long time that there are two main bacteriologic groups of cases of peritonitis: (1) those that seem to appear spontaneously and (2) those that occur by a spread of organisms of some of the contained viscera. In the first or primary group, the causative organisms are generally hemolytic streptococcus or pneumococcus. In the other or secondary group, the peritoneal exudate frequently yields a number of bacterial species. Most of the workers in this field have tried to find out which of the several species was the significant one. Malvoz [15] and also Laruelle [16] attributed the primary rôle to B. coli. Tavel and Lanz,[17] who made a very exhaustive bacterial study, but without adequate anaerobic technic, stressed the fact that many of the cases were polymicrobic. They found a streptococcus frequently, but C. welchii very rarely. Their results seemed to indicate that the polymicrobic infections offered a better prognosis than the monomicrobic, but their study included the primary as well as the secondary peritoneal infections. A little later Veillon and Zuber [18] made studies of peritoneal exudates and discounted

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16. Laruelle, L.: Etude bacteriologique sur les péritonitis par perforation, Cellule **5**:61, 1889.

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18. Veillon and Zuber: Recherches sur quelques microbes strictement anaérobies et leur rôle dans la pathologie humaine, Arch. d. méd. expér. et d'anat. path. **10**: 517, 1894.

the importance of the aerobes, laying particular stress on the anaerobes. These writers probably overemphasized the rôle of the anaerobes, but at least they called attention to them, and the recent workers have given them careful consideration. Heyde,[19] although he found B. coli to be the most frequent organisms in the peritoneal exudates that he studied, believed that it really played a subordinate rôle in the etiology of appendicitis and peritonitis. He laid more stress upon the gram-negative nonspore-forming anaerobic organism B. thetoides, although he was rarely able to demonstrate any pathogenicity of this organism in pure culture. Recently Weinberg and his associates[20] have reported studies of the purulent exudates in acute appendicitis. They received the appendixes in their laboratory, opened them from end to end and cultured the pus from the surface of the lesion. With this technic they could not avoid the intestinal organisms casually present, and it is difficult to evaluate their results on this account, but Weinberg takes a middle ground with respect to the significance of the aerobes and the anaerobes and brings out the possibility of a synergistic or symbiotic action of bacterial mixtures in the etiology of not only appendicitis but peritonitis. Weinberg found that in these exudates B. coli was by far the most common organism, occurring in 85 per cent. Intestinal streptococci were found in 30 per cent and Welch bacilli in 33 per cent. Anaerobic gram-negative bacilli were present in 39 per cent, and anaerobic cocci in 19 per cent. Although the aerobic species outnumbered the anaerobic in the whole series, the anaerobes predominated in the gangrenous cases, and Weinberg concluded that the gangrene was due to their presence. He found that the B. coli strains and the C. welchii strains were generally pathogenic for laboratory animals, but the other predominant organisms, previously mentioned, were for the most part innocuous when injected in pure culture. In association with the others, however, they seemed to become pathogenic themselves or to enhance the power of the associated organisms. Weinberg was handicapped by having no measure of the effect of the intestinal streptococcus when injected alone, as he found no pathogenic strains, but when small numbers were added to sublethal doses of B. coli or C. welchii, death insued. In our study of the peritoneal exudates,[1] our method differed from that of Weinberg, for his exudates, within the appendix, represented abnormal intestinal contents, while our cultures represented organisms that were able to survive the defensive forces of the peritoneum. We believe that our results,

19. Heyde, M.: Bakteriologische und experimentelle Untersuchungen zur Aetiologie der Wurmfortsatzentzündung (mit besonderer Berücksichtigung der anaëroben Bakterien), Beitr. z. klin. Chir. **76**:1, 1911.

20. Weinberg, M.; Prevot, A. R.; Davesne, J., and Renard, C.: Recherches sur la bactériologie et la sérothérapie des appendicitis aigues, Ann. Inst. Pasteur **42**:1167, 1928.

therefore, more nearly present the significant organisms in the peritoneal infection. The outstanding organisms in our series were B. coli, nonhemolytic streptococcus (a large group) and C. welchii. B. thetoides was only rarely found and was always nonpathogenic.

In cases of peritonitis such as one sees clinically there seems to be evidence that the infection is due to the organisms habitually present within the intestine rather than to the introduction of organisms not commonly found there. Mechanical accidents, such as a gunshot wound, a local ulceration or injury to the intestine from within or an interference of the blood supply of a part of the intestine, permit the organisms to invade the wall and pass through it into the peritoneal cavity. There is both clinical and experimental evidence to show that the peritoneum is able to overcome contamination with intestinal organisms provided that they are not introduced into the peritoneal cavity in too great numbers or at too great a speed, but if such limits are exceeded, peritonitis and death may ensue. In clinical cases, if there is no gross perforation of the wall, certain organisms may pass through the wall of the intestine or may be carried through by phagocytic cells in sufficient numbers for them to gain a foothold and multiply within the peritoneal cavity. Such organisms are of moderate pathogenicity. If there is a gross perforation of the intestine, numerous varieties of intestinal organisms, both pathogenic and nonpathogenic, enter the peritoneal cavity and not only may survive, but may multiply in this new environment. Usually only those of definite pathogenicity continue to multiply, and if the peritoneum finally gets the infection under control, one by one the different species that were originally present disappear from the peritoneal exudate. The survival of different species in the drainage tracts of peritoneal infections is being studied and will be reported later.

EXPERIMENTAL DATA

The present study has to do solely with the lethal effect of intraperitoneal injections into laboratory animals of the bacteria most frequently found in peritoneal exudates both in pure and in mixed cultures, namely, B. coli, nonhemolytic streptococcus and C. welchii.

Pathogenicity.—When these organisms are isolated and grown in pure culture and are injected into the peritoneal cavity of laboratory animals, it has been found that their pathogenicity varies considerably. When first isolated from the human body, minimal lethal doses of B. coli for guinea-pigs weighing 250 Gm. are in the neighborhood of 250,000,000, and for mice, 50,000,000. With C. welchii the intraperitoneal lethal dose is around 2,500,000,000 for guinea-pigs and 500,000,000 for mice. With streptococci very often doses of from 50,000,000,000 to 100,000,000,000 fail to kill guinea-pigs, while those

of from 10,000,000,000 to 20,000,000,000 often fail to kill mice. One of our strains, however, regularly killed when given in doses of between 5,000,000,000 and 10,000,000,000.

Bacterial Count.—The numerical estimate of bacteria was made with the Gates [21] turbidimeter, with a standard suspension of streptococci containing 2,000,000,000 to the milliliter as a control. The fact that B. coli is smaller and C. welchii larger than streptococci probably suggests that a relatively larger number of B. coli and a smaller number of C. welchii are necessary to attain the same degree of turbidity.

Increasing Virulence.—The virulence of our B. coli strains could very frequently be increased by repeated animal inoculations, and the minimal lethal dose was often lowered to 10,000,000 for guinea-pigs and 1,000,000 for mice. With C. welchii, repeated rapid animal inoculations very rarely increased the minimal lethal dose; in fact, it was usually better to pass it rapidly through artificial culture mediums than through animals. This is perhaps indicative of its essentially saprophytic nature. We could almost never increase the virulence of the intestinal streptococci. With all of these organisms, the minimal lethal dose varied from month to month, from week to week and even from day to day, and the variation in resistance of individual animals made quantitative experiments extremely difficult. This was true to a greater degree in guinea-pigs or rabbits than in mice because of the variation in size, weight and previous contact with infection. For the foregoing reasons any experiments depending on multiples, or fractions of, the minimal lethal dose are subject to variations in their results unless these changeable factors can be fairly adequately controlled.

Stabilizing Conditions.—The control of changeable factors is favored by using mice of approximately equal weight and by a determination of the minimal lethal dose of the organisms to be tested on the day preceding the experiment. It is important also to use only young cultures in a phase of active growth.[22] We have used in our experiments from four to eight hour cultures that are planted in the morning and injected in the afternoon, thus insuring the viability of a large proportion of the organisms injected. At first we had considerable difficulty with the virulence of B. coli. Finally we found that in almost every culture there are two types of colonies, one dark and the other pale, as seen by light transmitted through a blood agar plate. To reflected light, the dark colonies appear light, and the pale colonies appear dark. The light colonies by transmitted light are only slightly nonpathogenic, while the dark colonies maintain a fairly high and constant pathogenicity. It is important,

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22. Chesney, A. M.: The Latent Period in the Growth of Bacteria, J. Exper Med. **24**:387, 1916.

therefore, to transplant dark colonies initially into the broth from which the inoculation into the final culture is made. With C. welchii there are variations in the colonies that do not seem to have the same significance from the point of view of pathogenicity.

Source of Our Cultures.—We obtained our cultures of B. coli, green streptococcus and C. welchii from the exudate in an infected abdominal wound in a patient in whom a resection of the intestine had been performed. The initial pathogenicity of all of these organisms for mice and guinea-pigs was unusually high. The minimal lethal dose (M.L.D.)

TABLE 1.—*Intraperitoneal Injections of B. Coli and C. Welchii, Alone and Together* *

Mice	B. Coli	C. Welchii	Both		Result
			B. Coli	C. Welchii	
1	10 M	.....	.....	.....	Died over night
2	.....	800 M	.....	.....	Died over night
3	.....	.....	5 M	400 M	Died over night
4	5 M	.....	.....	.....	Died over night
5	.....	400 M	.....	.....	Died over night
6	.....	.....	2.5 M	200 M	Died over night
7	2.5 M	.....	.....	.....	Died over night
8	.....	200 M	.....	.....	Survived
9	.....	.....	1.25 M	100 M	Died over night
10	1.25 M	.....	.....	.....	Survived
11	.....	100 M	.....	.....	Survived
12	.....	.....	625 T	50 M	Died over night
13	625 T	.....	.....	.....	Survived
14	.....	50 M	.....	.....	Snrvived
15	.....	.....	313 T	25 M	Survived
16	.....	.....	156 T	12.5 M	Died over night
17	.....	.....	78 T	6.3 M	Sick; survived

M.L.D. in this test: B. coli, 2,500,000; C. welchii, 400,000,000

Fatal dose of mixtures: 1/2 M.L.D. of B. coli + 1/4 M.L.D. of C. welchii
1/4 M.L.D. of B. coli + 1/8 M.L.D. of C. welchii
1/16 M.L.D. of B. coli + 1/32 M.L.D. of C. welchii

* Previously estimated minimal lethal doses: B. coli, 5,000,000; C. welchii, 500,000,000. B indicates billion; M, million; T, thousand; M.L.D., minimal lethal dose.

for white mice of B. coli approximated from 1,000,000 to 5,000,000; of C. welchii from, 200,000,000 to 400,000,000, and of green streptococcus, from 1,000,000,000 to 10,000,000,000.

Method.—We made all of the four possible combinations with these three organisms, using two together and then all three together, and repeated the experiments several times with entirely consistent results. Tables 1 to 4 show the protocols of typical experiments. Our pure cultures were obtained by repeated plating and fishing, and the stock cultures were kept on cooked meat medium. Fresh inoculations were made from the stock cultures (or from dark colonies in the case of B. coli), two days before the day of the experiment, into cooked meat mediums with 0.2 per cent dextrose for overnight growth. In the morning these cultures were seeded into a fresh cooked meat medium with

TABLE 2.—*Intraperitoneal Injections of B. Coli and Green Streptococcus, Alone and Together* *

Mice	B. Coli	Green Streptococcus	Both: B. Coli	Both: Green Streptococcus	Result
1	10 M	.....	.....	.....	Died over night
2	.....	10 B	.....	.....	Died over night
3	.....	.....	5 M	5 B	Died over night
4	5 M	.....	.....	.....	Died over night
5	.....	5 B	.....	.....	Sick; survived
6	.....	.....	2.5 M	2.5 B	Died over night
7	2.5 M	.....	.....	.....	Died over night
8	.....	2.5 B	.....	.....	Survived
9	.....	.....	1.25 M	1.25 B	Died over night
10	1.25 M	.....	.....	.....	Died over night
11	.....	1.25 B	.....	.....	Survived
12	.....	.....	625 T	625 M	Died over night
13	625 T	.....	.....	.....	Survived
14	.....	625 M	.....	.....	Survived
15	.....	.....	313 T	313 M	Died over night
16	.....	.....	156 T	156 M	Died over night
17	.....	.....	78 T	78 M	Died in 40 hours

M.L.D. in this test: B. coli, 1,250,000; green streptococcus, 10,000,000,000

Fatal dose of mixtures: 1/2 M.L.D. of B. coli + 1/16 M.L.D. of green streptococcus
1/4 M.L.D. of B. coli + 1/32 M.L.D. of green streptococcus
1/8 M.L.D. of B. coli + 1/64 M.L.D. of green streptococcus
1/16 M.L.D. of B. coli + 1/128 M.L.D. of green streptococcus

* Previously estimated minimal lethal doses: B. coli, 5,000,000; green streptococcus, from 5,000,000,000 to 10,000,000,000. B indicates billion; M, million; T, thousand; M.L.D., minimal lethal dose.

TABLE 3.—*Intraperitoneal Injections of C. Welchii and Green Streptococcus, Alone and Together* *

Mice	C. Welchii	Green Streptococcus	Both: C. Welchii	Both: Green Streptococcus	Result
1	1 B	.....	.....	.....	Died over night
2	.....	15 B	.....	.....	Died over night
3	.....	.....	500 M	7.5 B	Died over night
4	500 M	.....	.....	.....	Died over night
5	.....	7.5 B	.....	.....	Died over night
6	.....	.....	250 M	3.75 B	Died over night
7	250 M	.....	.....	.....	Died over night
8	.....	3.75 B	.....	.....	Died, 22 hours
9	.....	.....	125 M	1.88 B	Died, 22 hours
10	125 M	.....	.....	.....	Survived
11	.....	1.88 B	.....	.....	Survived
12	.....	.....	62.5 M	0.94 B	Died, 36 hours
13	62.5 M	.....	.....	.....	Survived
14	.....	940 M	.....	.....	Survived
15	.....	.....	31.3 M	470 M	Died, 48 hours
16	.....	.....	15.6 M	235 M	Sick; survived
17	.....	.....	7.8 M	117 M	Died, 24 hours

M.L.D. in this test: C. welchii, 250,000,000; green streptococcus, 3,750,000,000

Fatal dose of mixtures: 1/4 M.L.D. of C. welchii + 1/4 M.L.D. of green streptococcus
1/8 M.L.D. of C. welchii + 1/8 M.L.D. of green streptococcus
1/32 M.L.D. of C. welchii + 1/32 M.L.D. of green streptococcus

* Previously estimated minimal lethal doses: C. welchii, 500,000,000; green streptococcus, from 5,000,000,000 to 10,000,000,000. B indicates billion; M, million; M.L.D., minimal lethal dose.

0.2 per cent dextrose and grown for from four to eight hours. Their number was then determined with the Gates turbidimeter, and dilutions were made in buffered phosphate broth for a preliminary determination of the minimal lethal dose. After the minimal lethal dose of the two organisms to be tested had been determined in a preliminary series of animals, on the next day another series was given injections of these organisms in pure and in mixed culture as follows: Number 1 in the

TABLE 4.—*Intraperitoneal Injections of B. Coli, C. Welchii and Green Streptococcus, Alone and Together*

Mice	B. Coli	C. Welchii	Green Streptococcus	All Three: B. Coli	All Three: C. Welchii	All Three: Green Streptococcus	Result
1	10 M	.....	.....	.....	.....	.....	Died over night
2	.....	1 B	.....	.....	.....	.....	Died over night
3	.....	.....	10 B	.....	.....	.....	Died over night
4	.....	.....	.....	3.3 M	0.3 B	3.3 B	Died over night
5	5 M	.....	.....	.....	.....	.....	Died over night
6	.....	0.5 B	.....	.....	.....	.....	Died over night
7	.....	.....	5 B	.....	.....	.....	Died over night
8	.....	.....	.....	1.7 M	167 M	1.7 B	Died over night
9	2.5 M	.....	.....	.....	.....	.....	Died, 40 hours
10	.....	0.25 B	.....	.....	.....	.....	Died over night
11	.....	.....	2.5 B	.....	.....	.....	Died over night
12	.....	.....	.....	0.8 M	83 M	0.8 B	Died over night
13	1.25 M	.....	.....	.....	.....	.....	Survived
14	.....	0.125 B	.....	.....	.....	.....	Survived
15	.....	.....	1.25 B	.....	.....	.....	Survived
16	.....	.....	.....	0.4 M	42 M	0.4 B	Died over night
17	0.63 M	.....	.....	.....	.....	.....	Survived
18	.....	63 M	.....	.....	.....	.....	Survived
19	.....	.....	0.62 B	.....	.....	.....	Survived
20	.....	.....	.....	0.2 M	21 M	0.2 B	Sick; survived
21	.....	.....	.....	0.1 M	10 M	0.1 B	Died, 48 hours
22	.....	.....	.....	50 T	5 M	50 M	Survived

M.L.D. in this test: B. coli, 2,500,000; C. welchii, 250,000,000; green streptococcus, 2,500,000,000

Fatal dose of mixtures:

1/6 M.L.D. of B. coli + 1/6 M.L.D. of C. welchii + 1/6 M.L.D. of green streptococcus

1/24 M.L.D. of B. coli + 1/24 M.L.D. of C. welchii + 1/24 M.L.D. of green streptococcus

* Previously estimated minimal lethal doses: B. coli, 5,000,000; C. welchii, 500,000,000; green streptococcus, 5,000,000,000. B indicates billion; M, million; T, thousand; M.L.D., minimal lethal dose.

series received something more than one minimal lethal dose of one organism. Number 2 received a corresponding dose of the other organism. Number 3 received one half of each of these. The fourth animal received one half of the original dose of the first organism. Number 5 received one half of the original dose of the second organism, and number 6, one half of each of these, and so on. When the doses of pure culture were well below the estimated minimal lethal doses, the last three or four animals received simply one half of the dose of the mixture used with the preceding animal in the series, until the dilution was carried down to small fractions of the minimal lethal dose. When

all three of the species were combined, the mixture contained one third of the dose of the pure cultures. Thus the variability of the minimal lethal dose was controlled, and the actual minimal lethal dose under the conditions of the experiment was determined.

Results.—In almost every experiment it was possible to demonstrate that the mixtures of the organisms produced a lethal effect in considerably smaller doses than the pure cultures. Tables 1 to 4 indicate clearly the results that we obtained with these organisms when injected into mice. It will be seen in table 1 that three small fatal doses of the mixture of B. coli and C. welchii contained:

½ M.L.D. of B. coli + ¼ M.L.D. of C. welchii,
¼ M.L.D. of B. coli + ⅛ M.L.D. of C. welchii,
and 1/16 M.L.D. of B. coli + 1/32 M.L.D. of C. welchii, respectively.

Table 2 shows that four small fatal doses of the mixture of B. coli and green streptococcus contained:

½ M.L.D. of B. coli + 1/16 M.L.D. of green streptococcus,
¼ M.L.D. of B. coli + 1/32 M.L.D. of green streptococcus,
⅛ M.L.D. of B. coli + 1/64 M.L.D. of green streptococcus,
and 1/16 M.L.D. of B. coli + 1/128 M.L.D. of green streptococcus, respectively.

Table 3 shows that three fatal doses of the mixture of C. welchii and green streptococcus contained:

¼ M.L.D. of C. welchii + ¼ M.L.D. of green streptococcus
⅛ M.L.D. of C. welchii + ⅛ M.L.D. of green streptococcus
and 1/32 M.L.D. of C. welchii + 1/32 M.L.D. of green streptococcus, respectively.

Table 4 shows that two fatal doses of the mixture of B. coli, C. welchii and green streptococcus contained:

1/6 M.L.D. of B. coli + 1/6 M.L.D. of C. welchii + 1/6 M.L.D. of green streptococcus and 1/24 M.L.D. of B. coli + 1/24 M.L.D. of C. welchii + 1/24 M.L.D. of green streptococcus, respectively.

COMMENT AND SUMMARY

We have experimented with the organisms commonly found in peritoneal exudates, namely, B. coli, nonhemolytic streptococcus and C. welchii, with the purpose of determining, if possible, their synergistic action in producing fatal peritonitis following intraperitoneal injection. We have determined the minimal lethal dose of each organism in pure culture and have found that the minimal lethal dose of B. coli when first isolated from either man or animals and injected intraperitoneally into animals is consistently less than the minimal lethal dose of C. welchii and considerably less than the minimal lethal dose of the intestinal streptococci. Furthermore, the virulence of B. coli may be increased by repeated animal inoculation, but C. welchii and the

intestinal streptococci are rarely amenable to this enhancement. While it is not proper to conclude that this relative pathogenicity in animals applies to man also, the foregoing facts are consistent with the clinical observations in our first paper, which indicated that C. welchii is not particularly virulent in the peritoneal cavity and that it is essentially saprophytic rather than pathogenic.

In order to achieve consistent results in experiments involving quantitative measurements, we found it necessary to stabilize conditions as far as possible. When dealing with organisms of low virulence, the effects of any variables are greatly magnified. In order to minimize the effects of variable factors, we took the following precautions: We made a preliminary determination of the minimal lethal dose of each organism just before the experiment in which it was used. We inoculated young bacterial cultures from four to eight hours old in an active growth phase and with the Gates turbidimeter made as accurate as possible a determination of the numbers of organisms present in the inoculum. We used enough animals in each experiment to be sure that moderate variations in the minimal lethal dose from day to day would not nullify the experiment. We used white mice of uniform size from the same brood. With these precautions our results were consistent.

We made all of the four possible combinations with the three species of organisms commonly found in peritoneal exudates. B. coli was combined with green streptococcus and with C. welchii. Green streptococcus was then combined with C. welchii, and lastly all three were combined. The experiments consisted of injecting intraperitoneally into a series of white mice constant multiples and constant fractions of the preliminary minimal lethal dose for each pure culture and each combination, and the lethal effects were observed. Tables 1 to 4 show that when any two or all three of these organisms were combined, the mixture was lethal in quantities considerably less than the lethal doses of the pure cultures. Death of the animals occurred with these mixtures in doses ranging from one-tenth to one-fifteenth of the lethal dose of the pure cultures.

The nature of this lethal effect has not been determined. It may be due simply to the growth-stimulating effect of one organism on the other, or it may indicate the production of some toxic product by the synergistic action of the combined organisms that neither can produce alone. The first explanation is not borne out by test tube experiments. In view of the other synergistic effects about which we know, the latter theory is quite within the range of possibility, but it is difficult to prove.

The tables further indicate that each species had an adjuvant effect on the other two, and in this respect no one species stands out as being more effective than the others. This corresponds strikingly with the clinical observations reported in the first paper and bears out the opinion

there expressed that, contrary to general belief, C. welchii is not more active than the other two organisms in peritoneal infections, and the consequences of its presence are not more serious.

CONCLUSIONS

The bacteria commonly found in peritoneal exudates, namely, colon bacillus, green streptococcus and Welch bacillus, have a synergistic action in producing a lethal infection of the peritoneum. They kill in much smaller doses when two or three of the species are combined than when inoculated in pure culture. The Welch bacillus is not more active in this synergistic action than the other two.

Smears and cultures of the peritoneal exudate should be made at the time of operation in cases of peritonitis in order that there may be a basis for prognosis. If the cultures reveal more than one species of intestinal organism, the prognosis is likely to be worse than if any one organism is found in pure culture. (This does not apply to the primary forms of peritonitis usually due to hemolytic streptococcus or pneumococcus.)

Any study of experimental or clinical peritonitis from a bacteriologic point of view must take into consideration not only the adjuvant action of one species of intestinal bacteria on the others, but the possibility of a toxic substance formed by the synergism of these bacteria when growing together in mixed cultures which may not be produced by any one of the species in pure cultures.

THE BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

IV. OBSERVATIONS ON A HIGH CARBOHYDRATE DIET

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In previous papers we have considered the effect of a standard diet [1] and of a high fat diet [2] on the breaking strength of healing fractured fibulae in albino rats. In our present paper we shall report the results of a study of the influence exerted on the breaking strength of similar fractures by a high carbohydrate diet.

The absorption of calcium and phosphorus from the gastro-intestinal tract has been shown to be favored by acidic intestinal contents.[3] Consequently the foods that produce such contents are advantageous in the assimilation of these salts. Lactose, for one, establishes acid-producing flora in the intestine, while corn starch changes the reaction of the tract but slightly.[4] In agreement with the changes in the hydrogen ion concentration produced by these two carbohydrates, it has been demonstrated experimentally that lactose increases the absorption of calcium and phosphorus, while starch diets are followed by inconsequential changes in the normal quantity of salts taken into the circulation from

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The expense of this investigation was defrayed by Davis and Geck, Inc.

1. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet, Arch. Surg. **24**:458 (March) 1932.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Lumsden, R. W.: The Breaking Strength of Healing Fractured Fibulae of Rats: III. Observations on a High Fat Diet, Arch. Surg. **25**:467 (Sept.) 1932.

3. Orr, W. J.; Holt, L. E., Jr.; Wilkins, L., and Boone, F. H.: The Relation of Calcium and Phosphorus in the Diet to the Absorption of These Elements from the Intestine, Am. J. Dis. Child. **28**:574 (Nov.) 1924. Irving, L., and Ferguson, J.: Proc. Soc. Exper. Biol. & Med. **22**:527, 1925.

4. Mitchell, H. S.: Am. J. Physiol. **79**:537, 1927.

the intestine.[5] Lactose, however, is poorly tolerated and results in clearly defined deleterious symptoms when fed in excess amount for a period of time.[6] Starch, on the other hand, satisfies the carbohydrate requirements, is well tolerated and permits a normal calcium and phosphorus metabolism.[5]

The metabolic correlation between the metabolism of carbohydrates and phosphorus has been shown by a number of workers[7] to be close. It has been demonstrated that the ingestion of a large amount of carbohydrate is followed by a sharp fall in the serum inorganic phosphate.[8] The disappearance of the phosphates is believed by these workers to be due to their combination with certain carbohydrates, forming among other compounds, hexose phosphates and glycerophosphates. It is these particular forms of phosphates that appear to be especially concerned in the hydrolytic reaction with the bone esterase phosphatase, the end-product of the reaction being phosphate in a form suitable for the growth, development and repair of bone.[9] One might assume from the foregoing data that an increase in the carbohydrate-phosphate compounds in the blood stream following the administration of a high carbohydrate diet would result in an increase in the reparative process of fractures due to the greater quantity of carbohydrate-phosphates available for hydrolysis by phosphatase. Our results are not, however, in accord with such an assumption.

The relationship existing between the metabolism of calcium and carbohydrates is not apparently as well understood as is that of phosphorus. We do know, however, that calcium and phosphorus tend to maintain a relatively constant ratio,[10] and that as the one varies the other likewise varies in an effort to maintain a constant balance.[11] Theoretically, it is possible that with a reduction in the organic phosphates of the serum, following ingestion of quantities of carbohydrates, the calcium would in turn be reduced through an increase in the amount of it excreted by the normal channels in an attempt to restore the ratio. Should this take place, healing of fractures under such conditions would be less complete than otherwise, and the breaking strength of the callus would be correspondingly reduced. In addition to the foregoing possi-

5. Bergeim, O.: J. Biol. Chem. **70**:35, 1926.

6. Block, C. E.: Brit. M. J. **1**:293, 1921.

7. Bolliger, A., and Hartman, F. W.: J. Biol. Chem. **64**:91, 1925. Harrop, G. A., and Benedict, E. M.: J. Biochem. **59**:683, 1924.

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9. Martland, M., and Robison, R.: Biochem. J. **23**:237, 1929. Kay, H. D.: ibid. **20**:798, 1926. Goodwin, H. W., and Robison, R.: ibid. **18**:1161, 1924.

10. Hoag, J. R., and Palmer, L. S.: J. Biol. Chem. **76**:367, 1928.

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bility, it has also been shown that the hypoglycemic state of parathyroid tetany can be obviated by injections of calcium salts, as well as by solutions of dextrose.[12]

Some interdependence between carbohydrate and calcium metabolism evidently does exist, but we are in possession of little experimental knowledge concerning it.

PROCEDURE

The routine technic adopted for this series of studies has been given in detail before.[13] The Moise and Smith high carbohydrate diet[14] was used in this investigation. Corn starch furnishes the elevated carbohydrate percentage, and was the most suitable form for our purposes.

In addition to this diet, 100 mg. of dried yeast powder was fed every second day. The salt mixture was the same Osborne and Mendel[15] preparation described in former papers, but differed in being 0.8 per cent less in quantity than in the standard diet, and 2.8 per cent less than in the high fat food. The differences in the quantity of salt in each of the foregoing diets were due to the known

High Carbohydrate Diet

	Percentage	Calories per Kilogram of Food		Apportionment of Total Calories
Casein	14.0	514	Protein	13.8
Starch (corn)	79.0	3,239	Carbohydrate	77.8
Cod liver oil	3.8	353	Fat	8.4
Salts	3.2			
		4,166		

differences in the amounts of the various diets that the animals would consume. Smith and Carey[16] established this fact several years ago when they showed that rats ate for calories. They adjusted the salt content of their diets in such a fashion that, regardless of a reduction or an elevation in the ingestion of the particular diet under study, the amount of salt taken in remained comparatively constant. Owing to this correction, it is permissible to consider the salt intake on each of the three diets to be relatively the same.

At the expiration of one week on the diet, the animals were divided into two groups. The first group, known as the "high carbohydrate fracture," was divided into fourteen lots of seven animals to each lot. The right fibula of every animal in this group was fractured in the manner described before,[13] and beginning on the sixth postoperative day and continuing at intervals of three days thereafter for the fourteen time periods, the entire lot of seven on that particular time period was killed. After suitable preparation the breaking and healing strengths of the unfractured left and the fractured right fibulae, respectively, were determined in the manner described before.[13]

12. Cori, C. F., and Cori, G. T.: J. Biol. Chem. **79**:321, 1928. Reed, C. I.: Am. J. Physiol. **89**:230, 1929.

13. McKeown, Lindsay, Harvey and Howes (footnote 1). McKeown, Lindsay, Harvey and Lumsden (footnote 2).

14. Moise, T. S., and Smith, A. H.: J. Exper. Med. **40**:13, 1924.

15. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **37**:557, 1919.

16. Smith, A. H., and Carey, E.: J. Biol. Chem. **53**:425, 1923.

The second group, called the "high carbohydrate control" to distinguish it from the fractured group, was free from fractures and had also been on the diet for one week. At the same time the fibulae were fractured in the fractured rats, this second group was divided into lots of four, and a lot placed on each of the fourteen time periods from the sixth to the forty-fifth postoperative days. Thus, there were eleven rats on every time interval, seven having fractured right fibulae and four being free from fractures. The controls served to adjudge the effect of the diet alone on the normal breaking strength of rat fibulae.

In the second paper of this series,[1] we determined the breaking strength of normal rat fibulae, in addition to the healing strength of fractured rat fibulae, in animals on a standard diet. The data obtained at that time are used throughout our present paper to evaluate the observed results. Relative metabolic studies on animal weight and food intake were again prepared, and representative roentgenograms of the healing fractures from interval to interval, as well as correlations between animal weight, fibular length and fibular strength, were made once more. Further, a gross examination of the callus was performed in an effort to add additional information to that obtained.

RESULTS

To avoid confusion, the control and fracture groups are considered separately.

TABLE 1.—*Correlation Between the Fibular Length and the Fibular Strength for the High Carbohydrate Controls* *

	Fibular Length									
	2.0 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean	316	309	326	306	491	471	509	505	570	580
Combined arithmetic mean	313		316		481		507		575	
Normal normal combined arithmetic mean	384		450		457		509		†	
Standard diet control combined arithmetic mean	303		308		394		526		482	
High fat diet control combined arithmetic mean	309		398		492		539		635	

* Refer to table 1a for complete data. † None of this length.

1. *The High Carbohydrate Controls.—A.* Correlation, (1) Between Fibular Length and Fibular Strength: The fibulae were divided into length groups as before,[13] and the respective breaking strengths of the right and left bones for each rat in each length group were placed under its particular division. It will be observed in table 1 that once more a positive correlation was obtained. Apparently, as the fibular length increases, the fibular strength likewise becomes greater.

(2) Between the Fibular Length and the Animal Weight: The fibular length divisions used previously were again utilized. The respective weight of each rat in the group was placed under each length division, and the arithmetic mean obtained for each division again indicated that the longer the animal's fibula the heavier the animal would be (table 2).

(3) Between the Weight of the Animal and the Length of Its Fibula: The arbitrary weight divisions used earlier in these studies [13] were again made use of, and the fibular breaking strength of each mem-

TABLE 2.—*Correlations Between the Fibular Length and the Animal Weight for the High Carbohydrate Controls* *

	Fibular Length				
	2.0 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.	2.4 Cm.
Arithmetic mean	196	217	241	261	275
Normal normal arithmetic mean	209	230	251	284	†
Standard control arithmetic mean	214	223	233	278	295
High fat arithmetic mean	201	215	256	274	293

* Refer to table 2a for complete data. † None at this length.

TABLE 3.—*Correlation Between the Weight of the Animal and the Strength of Its Fibula for the High Carbohydrate Controls* *

	Weight Groups							
	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean	325	318	415	409	497	515	598	580
Combined arithmetic mean	322		412		506		589	
Normal normal combined arithmetic mean	401		415		498		564	
Standard diet control combined arithmetic mean	296		373		580		516	
High fat diet control combined arithmetic mean	332		443		481		589	

* Refer to table 3a for complete data.

TABLE 4.—*Breaking Strength Ratios of High Carbohydrate Diet Controls* *

Postoperative Days Observed	Left Fibular Ratio	Right Fibular Ratio
6	205±11	219± 8
9	239±33	235±35
12	232±13	257±13
15	289±20	274±16
18	269±38	286±42
21	232±17	222±25
24	242±29	238±37
27	190± 3	165±17
30	175±16	185±21
33	200±21	173±22
36	178±18	173±17
39	269±48	270±53
42	257±10	269±10
45	210±35	201±14

* Refer to table 4a for complete data.

ber in each division was recorded. It is evident from the means in table 3 that the heavier the animal the stronger is its fibula.

B. Fibula Breaking Strength Ratios: The breaking strength of the left and right fibulae of the four controls in each of the fourteen time

periods was determined as before.[13] Correction was then made by use of the formula [1]: $R = \frac{F}{(10.W)^{2/3}}$, and the results were tabulated in table 4, together with the standard deviation of the mean.

The left fibula was seen to be slightly stronger than the right, as it had been on the two diets studied before.[13] In figure 1 it will be noted that this difference is not constant, but over the duration of the experiment it is relatively so.

On the standard diet [1] it will be recalled that with the exception of a temporary rise above the normal breaking strength band on the twenty-fourth and twenty-seventh days, the strength diminished from

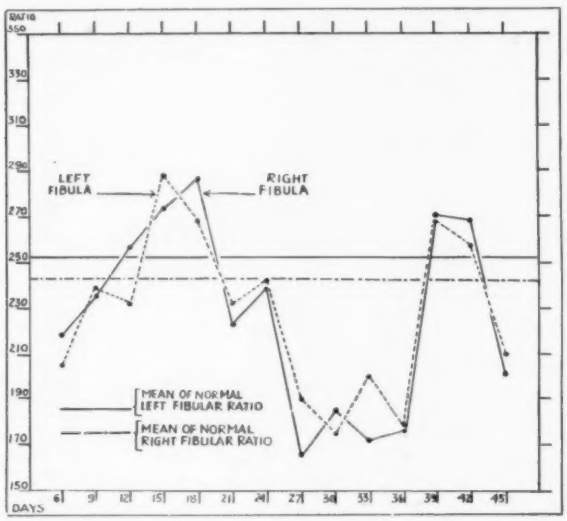

Fig. 1.—The breaking strength ratio of the left and right fibulae, with a normal ratio band. The high carbohydrate control group was entirely free from fractures. There was a slight increase in the strength of the fibulae during the early part of the experiment. Later strength was lost for a time, to be later regained and again lost. Strength was maintained somewhat better on this diet than on those described before. The left fibula was once more found to be stronger than the right.

the beginning to the end of the experiment in the control rats. The high fat diet controls, on the contrary, will be remembered to have shown wide fluctuations both above and below the normal band.[2] The trend of the breaking strength in the fat controls was, however, found to be slightly above normal. In the high carbohydrate control rats, as shown in figure 1, the breaking strength first increased, then diminished, again rose and again fell. The trend of the curve may be said to have been a primary rise followed closely by a secondary fall. Fibular strength in the control rats on the carbohydrate diet did not vary so sharply or

so frequently as it did on the fat diet, or so abruptly as on the standard. It did resemble the strength of the standard diet controls, though more in its tendency to decrease than to increase. Normal strength was probably better maintained on the high fat diet than on either the standard or the high carbohydrate diet.

C. Relative Data on Animal Weight and Food Ingestion: The animal weights fell from the onset of the experiment (table 5). This loss was not uniform, but the curve of weight in figure 2 is seen to drop throughout. Figure 2 also shows that somewhat the same loss in

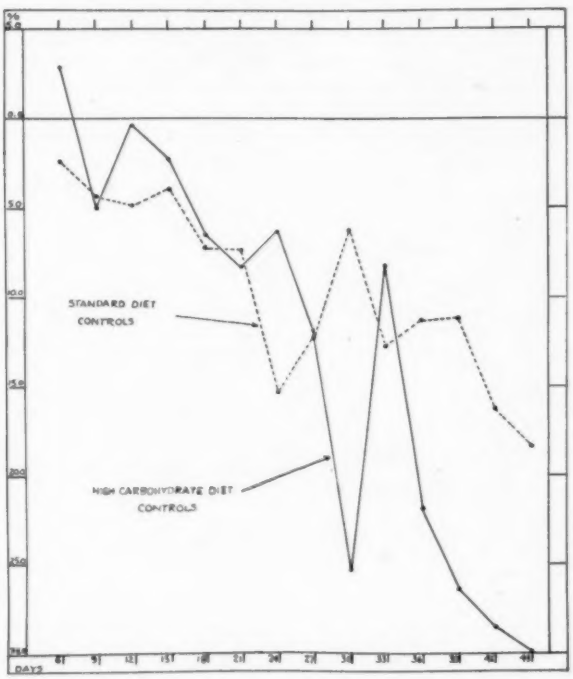

Fig. 2.—Difference in weight from operation to death, plotted as percentage of body weight at operation for the high carbohydrate and standard diet controls. The weight was at first comparatively well maintained on the high carbohydrate diet by the control animals, but later the rats were unable to reach the weights established by the standards on a standard diet.

weight occurred on the standard diet during the earlier part of the experiment. After the twenty-first day, however, the loss of weight was greater on the carbohydrate diet than it had been on the standard. Of the three diets so far reported, weight was more successfully maintained on the high fat diet [2] than it was on the standard or the high carbohydrate diet. Consequently, a greater loss occurred on the carbohydrate diet than on either the standard or the fat diet.

TABLE 5.—*Animal Weights and Food Intakes for the High Carbohydrate Controls* *

Postoperative Day	Difference in Weight from Operation to Sacrifice as Percentage of Weight at Operation	Food Consumed per Day from Operation to Sacrifice as Percentage of Weight at Operation
6	+ 2.9	9.2
9	— 5.1	6.7
12	— 0.4	5.5
15	— 2.2	4.7
18	— 6.5	5.8
21	— 8.2	6.2
24	— 6.3	5.9
27	—11.9	5.6
30	—25.1	4.9
33	— 8.1	5.3
36	—21.9	3.7
39	—26.2	3.6
42	—28.5	4.8
45	—30.0	4.5

* Refer to table 5a for complete data.

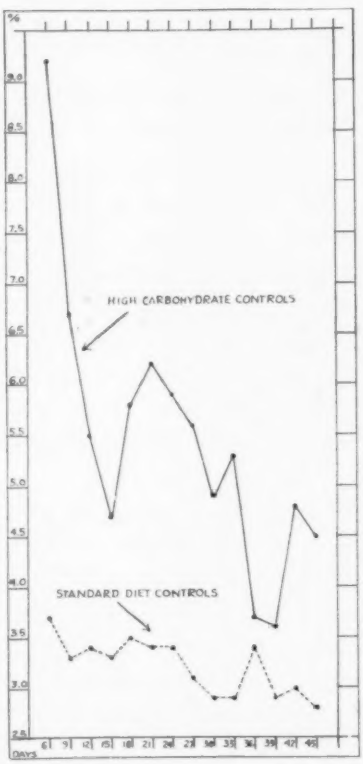

Fig. 3.—Food consumed per day, plotted as percentage of body weight at operation, for both the high carbohydrate and standard diet controls. The larger quantity of food consumed on the high carbohydrate diet is evident from the upper curve. Although the amount diminished over the extent of the experiment, it still remained higher than that eaten on the standard diet.

TABLE 6.—*Calories Consumed per Day from Operation to Sacrifice by Control Rats on a Standard Diet, a High Carbohydrate Diet and a High Fat Diet*

Postoperative Days	Standard Diet Controls	High Carbohydrate Diet Controls	High Fat Diet Controls
6	53.40	79.16	34.03
9	55.56	59.99	45.47
12	42.72	59.16	34.09
15	37.38	51.66	46.14
18	38.98	55.83	35.03
21	45.93	56.66	54.33
24	49.13	51.24	36.47
27	40.00	47.08	43.91
30	36.85	43.33	50.61
33	36.85	45.83	49.86
36	41.12	36.66	50.60
42	40.06	44.16	41.30
45	38.45	39.58	42.42

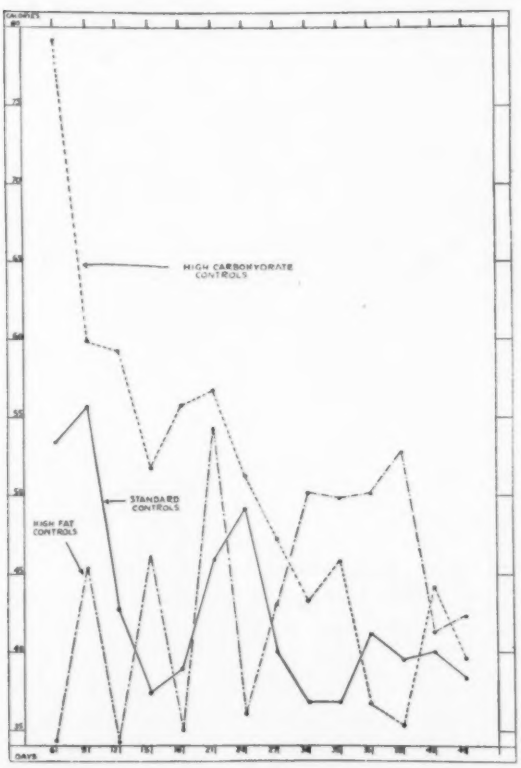

Fig. 4.—Calories consumed per day from operation to death by control rats free from fractures on a standard, a high fat and a high carbohydrate diet. The control animals consumed more calories on the high carbohydrate diet than on the standard or the high fat diet.

The quantity of food consumed on the high carbohydrate diet was greater than it had been on either the standard or the high fat diet. In figure 3 it is noted that although the amount taken by the animals fell after a short period of time, it nevertheless remained definitely more than on the standard diet. We have already observed [2] that on the high fat diet less food was eaten than on the standard, hence we are led to conclude that more of the carbohydrate diet was ingested by the animals than of either the standard or the high fat diet.

Calorically, the high carbohydrate diet afforded 4.166 calories per gram; the standard diet, 5.340 calories per gram, and the high fat diet, 7.442 calories per gram. The truth of Smith and Carey's [16] finding, that rats eat until their caloric demands are satisfied becomes evident when we consider our results on body weight and food intake. We saw that the quantity of the carbohydrate diet consumed was greater than that of either the standard or the high fat diet. The necessity for this is apparent when we note that the carbohydrate diet offers less calories per gram than does either of the other two diets.

The caloric intakes for the control animals on the three diets have been tabulated in table 6 and plotted in figure 4.

11. *High Carbohydrate Fracture Group.*—The left fibula in these animals was not fractured, while the right was fractured as before at a point opposite the tibial prominence.[13] Owing to the obvious differences between the two fibulae, their breaking strengths are considered separately.

A. Unfractured Left Fibular Breaking Strength Ratio: As in all previous studies, the breaking strength determinations were begun on the sixth and continued to the forty-fifth postoperative day.[13] A minimum of five observations was recorded for each of the fourteen time periods.

A rise in the ratio was noted on the twelfth day, which was three days earlier than a similar rise that occurred on the standard diet. The height reached was, however, about 90 lower than that found for the standard at its peak on the fifteenth day. An immediate fall in the ratio of the carbohydrate left fibula took place subsequent to the rise, as it had also done in the standard left. The low point reached by the carbohydrate on the fifteenth day was, however, 10 less than that attained by the standard on the twenty-first day. Thereafter, the ratio of the carbohydrate left fluctuated widely, but showed throughout a persistent reduction in its strength until by the forty-fifth day the ratio was 100 less than that observed for the standard on the same day. The ratios in table 7 have been plotted in figure 5.

TABLE 7.—*Breaking Strength Ratios of Unfractured Left and Fractured Right Fibulae on a High Carbohydrate Diet* *

Postoperative Day	Unfractured Left	Fractured Right
6	199±6	12±10
9	208±32	76±19
12	243±28	102±12
15	182±17	107±19
18	201±32	101±7
21	278±19	108±16
24	240±24	102±22
27	208±17	132±24
30	183±9	151±14
33	222±26	142±11
36	175±13	115±14
39	157±8	103±19
42	188±29	146±19
45	160±25	145±23

* Refer to table 7a for complete data.

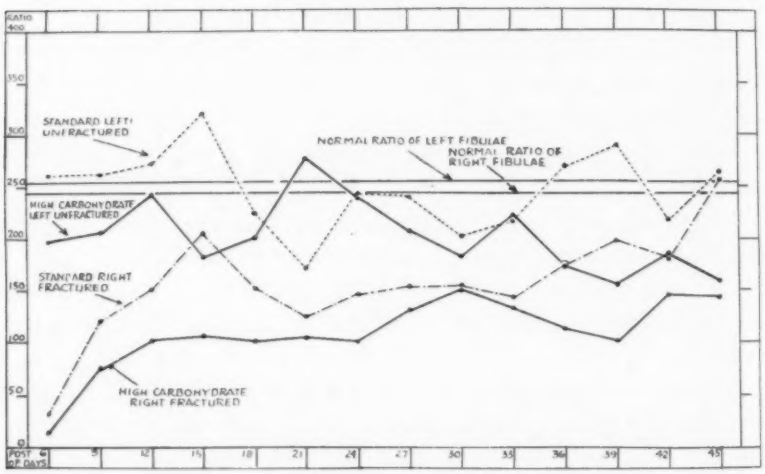

Fig. 5.—Ratio of healing strength of fractured right fibulae and breaking strength of unfractured left fibulae in high carbohydrate fracture group, with similar ratios for standard diet fibulae. The band represents the breaking strength ratios of fifty normal right and left fibulae. The primary callus was formed on the high carbohydrate diet by the fifteenth day as it had been on the standard diet. However, the subsequent drop due to the formation of the medullary space did not take place on the carbohydrate diet as it had on the standard diet. The unfractured left of the carbohydrate fractured group fluctuated in strength as the left of the standard diet did. This was thought to be due to the variable demands made on the left for salts with which to supply the fracture in the right fibula. The end-point was about 30 per cent lower than that attained by the standards.

B. Fractured Right Fibular Ratio: On the standard diet it was established that there are three particular points of interest on the curve of healing strength. These are the time at which the primary callus is formed, as shown by the first peak in the curve; the time at which the medullary space is formed, as shown by the sharp loss in strength subsequent to the formation of the primary callus, and the time taken to restore the strength of the fracture to that of the unfractured fibula on the opposite leg. In the standard diet we found the primary callus formed by the fifteenth day, the medullary space particularly active in its

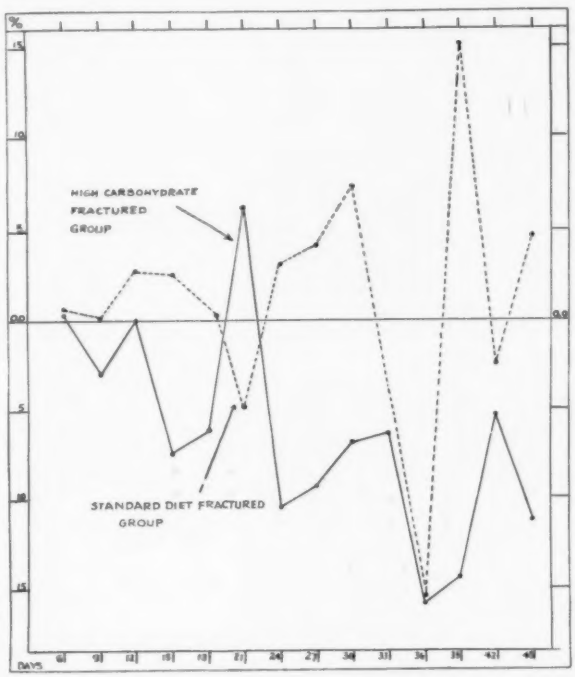

Fig. 6.—Difference in weight from operation to death, plotted as percentage of body weight at operation for the high carbohydrate and standard diet fractured groups. The high carbohydrate fractured group did not maintain the weight as successfully as did the standard fractured group. The early gain in weight during the first fifteen days on the standard diet, which was believed to be due to the increased metabolism as a result of the fracture, was not observed to occur on the high carbohydrate diet until twelve days later.

formation between the fifteenth and the twenty-first days and the endpoint reached by the forty-fifth day.

In the carbohydrate diet the primary callus was also considered as having been formed by the fifteenth day, but it had a ratio 101 less than the standard and 5 less than the high fat on the same time period. The

fall noted to have occurred concomitantly with the gross appearance of the medullary cavity in the standard and the fat diets did not take place on the carbohydrate diet. On the contrary, it will be seen in table 7 and figure 5 that the ratio remained relatively constant from the fifteenth to the twenty-first day. This was within the time limits established by the standard diet, and three days later than that established by the high fat diet. The ratio for the carbohydrate fractured right on the forty-

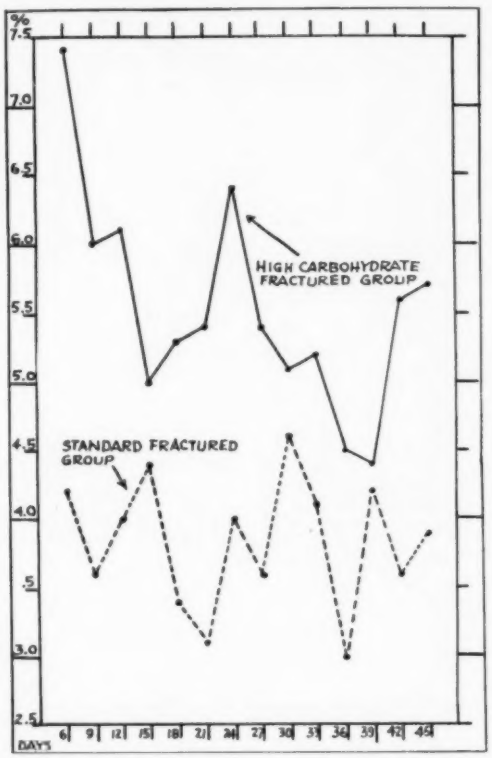

Fig. 7.—Food consumed per day, plotted as percentage of body weight at operation for both high carbohydrate and standard diet fractured groups. More food was consumed by the rats with fractured fibulae on a high carbohydrate diet than those on a standard diet.

fifth day was, however, 120 less than that for the standard right, and about 60 less than the high fat right.

C. Weight of Rats and Food Consumption: With the exception of a sharp rise on the twenty-first day, the weights fell from the beginning to the end of the experiment. The fall was not as rapid or as complete as it had been in the case of the carbohydrate controls, but it was more so than it had been in the standard fractures. A sugges-

tion of a moderate increase in body weight, in response to an acceleration of metabolism as a result of the injury induced by the fracture, may be noted in table 8 and figure 6. The weights of the rats remained in closer proximity to normal during that interval, and did not continue to fall until later.

The rats on a high carbohydrate diet with fractured fibulae consumed more food throughout than did the standards (table 8 and fig. 7). Despite this we have already seen that the weights of the animals fed carbohydrate decreased more than those of the standards. It was observed, as it had been before, that as the quantity of food consumed fluctuated, the weights of the animals did likewise. As one fell the

TABLE 8.—*Animal Weights and Food Intakes of Fractured Animals on a High Carbohydrate Diet* *

Postoperative Day	Difference in Weight from Operation to Sacrifice as Percentage of Weight at Operation	Food Consumed per Day from Operation to Sacrifice as Percentage of Weight at Operation
6	+ 0.4	7.4
9	— 3.0	6.0
12	0.0	6.1
15	— 7.5	5.0
18	— 6.1	5.3
21	+ 6.4	5.4
24	—10.5	6.4
27	— 9.3	5.4
30	— 6.9	5.1
33	— 6.4	5.2
36	—15.7	4.5
39	—14.4	4.4
42	— 5.2	5.6
45	—11.1	5.7

* Refer to table 8a for complete data.

other also fell, and as the one rose, the other also rose. The diminution in the amount of food ingested and the loss in body weight of the rats may at least partially account for the loss in strength in the unfractured left fibula, for it was found earlier in this paper that body weight and fibular strength were positively correlated. It is conceivable that as weight was lost on the carbohydrate diet, the strength of the left fibula became less.

The calories consumed per day on the high carbohydrate diet would be expected to agree in the character of their plotted curve with the curve of the quantity of food consumed per day. Such proved to be the case. It may be seen in table 9 that the animals ate more calorically of the high carbohydrate diet than of either the standard or the high

fat diet. The curve for the carbohydrate calories in figure 8 is also at a consistently higher level than it is on the other two diets.

D. Roentgenographic Studies: The density of the callus increases to the twenty-fourth day, following which a moderate degree of rare-

TABLE 9.—*Caloric Intake per Day from Operation to Sacrifice for the Standard, the High Carbohydrate and the High Fat Fractured Animals*

Postoperative Day	Standard Diet Fractured Animals	High Carbohydrate Fractured Animals	High Fat Fractured Animals
6	23.37	30.83	23.51
9	19.22	24.99	14.66
12	21.36	25.41	20.24
15	23.50	20.83	20.24
18	18.16	22.07	24.55
21	16.55	22.49	22.10
24	21.36	26.66	19.50
27	19.22	22.49	18.30
30	24.56	21.25	17.63
33	21.89	21.66	16.24
36	16.02	18.75	20.46
39	22.43	18.33	18.60
42	19.22	23.33	26.04
45	20.83	23.75	20.24

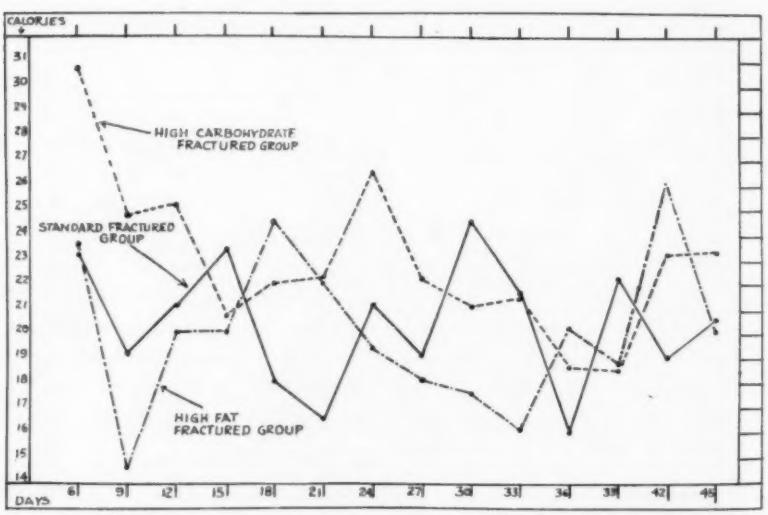

Fig. 8.—Caloric intake per day from operation to death for the standard, high carbohydrate and high fat fractured groups. In addition to eating more food, the high carbohydrate fractured animals ate more calories than on any diet previously studied.

faction becomes evident (fig. 9). The formation of the medullary space, suggested on the standard and fat diets by a reduction in the density between the fifteenth and the twenty-first days, was not so clearly seen in the carbohydrate fractures. Subsequent to the thirtieth day, the size of the callus was much less than it had been in the standard fractures, and this may at least partially explain the lowered strength apparent in it at that time. The reorganization of the bony contour of the diaphysis is well shown in figure 9, as is the reduction in its size. By the time the end-point had been reached on the forty-fifth day, the shaft

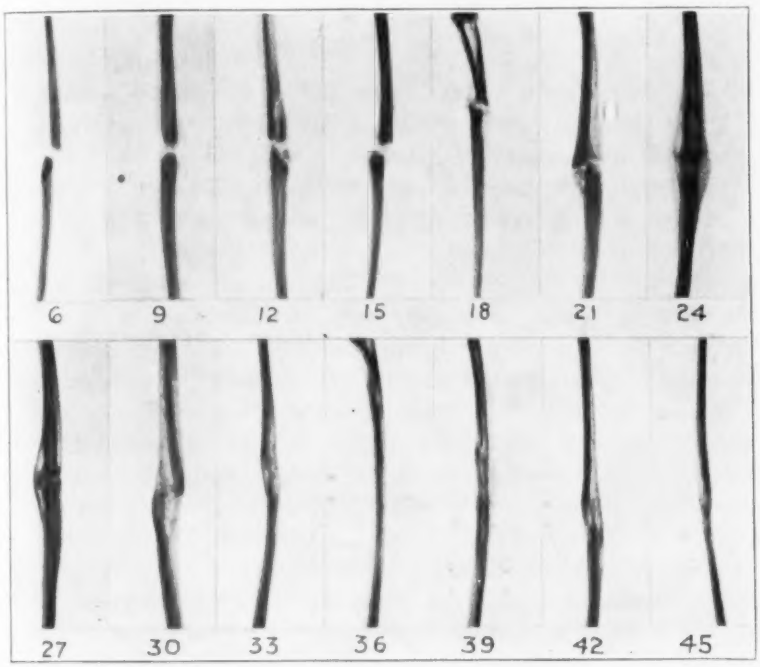

Fig. 9.—The roentgenograms taken of representative fractures in the high carbohydrate fracture group in each of the fourteen time periods studied again demonstrated the inaccuracy of attempts to correlate healing strength with the roentgenographic picture. Strength from the fifteenth day on changed but little, yet the image noted in the roentgenograms varied a great deal. The soft and proliferating tissue between the fracture ends does not appear in the roentgenograms unless calcified, but it possesses, nevertheless, a high degree of breaking strength; × 3½.

of the fibula was a mere splinter, and one can readily understand its low strength ratio.

E. Gross Examination of the Callus: After the breaking strength determinations had been made, the separated proximal and distal fragments were mounted in blackened corks in such a manner that the calluses could be examined end-on beneath a dissecting microscope.

The delayed formation of the primary callus was evident at once, as was the retarded appearance of the medullary space. The diameter of the callus was observed to be below normal; the diameter of the medullary space was reduced, and the cortex was relatively thicker throughout than it had been in the standard calluses. Apparently the factors going to form the medullary space were less active on the carbohydrate diet. The histologic studies, in course of preparation, should aid our interpretation of the cytologic reaction of the healing fractures to the high carbohydrate diet.

COMMENT

For the third time it has been possible to demonstrate correlations between animal weight, fibular length and fibular breaking strength on the control animals. For the present, at least, we are apparently able to accept these correlations in toto.

If we may judge the efficiency of the diet on the basis of the breaking strength of the control rat fibula, we are led to believe that the high carbohydrate diet produces the greatest loss in fibular strength, while the high fat diet produces the least and the standard diet adopts an intermediate point. The diets were originally calculated by Moise and Smith,[14] from work previously done by Smith and Carey,[16] in such a manner that, although the quantity of food eaten by the rats differed with the diet offered, the salt intake would be essentially the same for each. Consequently we are not entirely justified in assuming that the variations from the normal breaking strength observed in the carbohydrate controls are due to differences in salt intake. Rather, we must consider, among other things, the possibility of an increase in the absorption of carbohydrate being followed by a reduction in the phosphates of the blood stream. Such a condition may result in an increase in the excretion of calcium to compensate for the reduction in available phosphates; it may diminish the quantity of phosphates suitable for repair of bone by putting them in such a form that they are not utilizable, or, on the contrary, it may even increase the available phosphates and reduce the quantity or activity of the bone esterase phosphatase. Studies on blood chemistry in connection with these diets are to be published at a later date, and will, it is hoped, add to our knowledge of the factors concerned in the loss of fibular strength in normal control rats on a high carbohydrate diet.

In the fibulae with fractures, the healing strength did not attain the level reached by either the high fat or the standard diet fractures on the fifteenth day. It did, however, show its first peak at that time, and this was interpreted as evidence that the provisional callus had formed within the normal time limit. The loss in strength immediately following the fifteenth day, seen in former dietary studies and attributed to the

rapid development of the medullary space during that interval, did not occur on the carbohydrate diet. Subsequently, the strength of the fracture on the carbohydrate diet became only slightly greater, and, in fact, reached an end-point on the forty-fifth postoperative day with a ratio of healing strength only 40 above that reached by its primary callus on the fifteenth day. The fracture healed in the time limits set by the standard diet fractures, but it did so at the expense of the strength of the unfractured left fibula.

The unfractured left fibula, in rats on a high carbohydrate diet with fractured right fibulae, increased slightly in strength during the first part of the experiment. This was thought to be due to a systemic increase in the metabolic elements creating bone strength. Among them we considered phosphatase as a possibility. Phosphatase occurs in the serum and bone in amounts above normal during the early stage of fracture healing,[17] and may explain the increased strength in the left fibula through the stage of primary callus formation. The lower height reached by the left fibula on the carbohydrate diet, as compared with the greater height reached by the left fibula on the standard diet, might be considered as additional evidence of either a diminution in the available phosphates; the presence of phosphates in normal amounts, but in a form on which phosphatase cannot act, or as a reduction in the phosphatase itself. Suffice it to say at this time that the strength of the left fibula varies after the provisional callus has been formed in proportion to the demands made on it by the healing fractured right fibula.

In no respect have we attempted to make detailed studies of the metabolism of the rats on the different diets. Rather, our prime consideration has been the effect of the diet on the healing strength of the fibula. However, several interesting features have developed in the studies we have made.

We have observed in the control animals free from fracture that the heavier the rat the stronger its fibula. Along the same line it was seen in the fracture animals that, within certain limitations, the strength of the fibula became greater as the weight of the rat increased, and fell as the weight diminished. It is quite true that this was but one of the many factors concerned in the reparative process, but it is nevertheless one of some importance. Healing of the fractured right fibula was completed within the time limits established on the standard diet, but was completed at the expense of the unfractured left fibula. Coincidentally, body weight dropped even as the strength of the unfractured left fibula became less. It would appear not unreasonable that part of the loss in strength of the left fibula was due to the presence of some inhibitory substance in the diet resulting in the inability of the left fibula to maintain its normal strength in the face of demands for healing

17. Kay, H. D.: J. Biol. Chem. **99**:249, 1930.

substances being made on it by the fractured right, or, on the other hand, its diminishing strength may have been due to a lack of some substance in the diet which was necessary for the repair of the fracture and which could be furnished only by the left fibula. Body weight and food intake are seemingly better indexes of the progress of the healing of fractures than we have previously believed.

The roentgenographic studies, although the interpretations that we are enabled to put on them are purely relative, are still of value. They afford a basis on which to estimate, somewhat roughly it is true, the degree or extent of the calcific process at any given time. They do not, however, show the organic material present about the callus, and it is this material with which we find ourselves chiefly concerned in the earlier stages of repair. An appreciable strength has been found in callus formed primarily of fibrous tissue which roentgenograms had previously led us to believe would have little if any strength. The roentgenogram has also been found to be an unsatisfactory method for determining the appearance of the medullary space, and for showing details of cortical thickening and reorganization. Possibly a more highly developed technic would obviate the difficulties that have arisen in connection with our use of the x-rays, but we are of the opinion at this time that they afford at best only a very relative index of callus strength and the course of the reparative process.

SUMMARY

1. Correlations on control rats, free from fractures, on a high carbohydrate diet have shown that on an average the heavier the animal, the longer and stronger its fibula will be. The reverse was also found to be true.

2. The breaking strength of the fibulae of the carbohydrate control rats was less than that of either the standard or the high fat diet control animals.

3. The breaking strength of the left fibulae in the carbohydrate controls was slightly greater than that of the right fibulae.

4. Body weight was maintained in the carbohydrate controls during the first twenty-one days at a level at least equal to that observed in the standard diet controls. Subsequently, the carbohydrate controls lost more weight than the standards.

5. The quantity of food consumed per day, as well as the calories consumed per day, by the carbohydrate control rats was uniformly greater than that ingested by either the standard or the high fat diet control animals.

6. In the animals on a high carbohydrate diet with fractured right fibulae, the primary callus was formed by the fifteenth day, but possessed less strength than did the calluses of the standard and the high fat fractures observed at the same interval.

7. The sharp drop in strength noted after the fifteenth day in the standard and the high fat fractures, which was believed to be due to the appearance of the medullary space, did not occur on the high carbohydrate diet. Grossly, it was seen that the medullary space was less completely formed and the cortex of the shaft was relatively thicker during the time medullary cavitation should have been developing, in the calluses of rats on a carbohydrate diet, than it had been in the calluses of rats on either the standard or the high fat diet.

8. The end-point was reached by the healing fracture on the carbohydrate diet by the forty-fifth day, which was within the limits established by the standard diet. Strength was, however, definitely less than on the standard or the high fat diet.

9. The unfractured left fibulae of rats on a high carbohydrate diet where the right fibula had been fractured, first increased in strength and then diminished, until by the forty-fifth day the strength was considerably lower than it had been in the case of the left fibulae of rats on a standard diet. The early rise in the left fibular strength was believed to be associated with the formation of the provisional callus in the fractured fibula of the opposite leg, and it was thought that the simultaneous variations in the curves of the left unfractured fibula alone indicated the repair of fractures to be a generalized phenomenon, and not one purely local in character. Thereafter, the loss in strength in the left fibula was possibly due to demands made on its constituents of strength in an effort to meet the lack of essential substances in the diet necessary for the repair of the fracture in the right fibula, or to overcome the presence of dietary products inhibitory to the successful healing of the fracture.

10. Roentgenographic studies of representative calluses over the course of the investigation indicated once more that x-rays afford an unsatisfactory means by which to determine callus strength at any given interval, or with which to obtain detailed knowledge of the stages of healing in the fracture.

CONCLUSIONS

A high carbohydrate diet, in which the protein and the salt requirements were satisfied, was fed rats with healing fractured right fibulae. Determinations of the breaking strength of the calluses were made at intervals of three days. The primary callus was observed to form within the normal limit of fifteen days, but it was seen to possess less strength than did calluses of animals on standard and high fat diets. The normal loss in strength occurring immediately after the formation of the provisional callus and held to be due to the formation of the medullary space was not noted in rats on the carbohydrate diet. The end-point was reached on the forty-fifth day, which was within the

normal time limit. Strength was, however, less than in either the standard or the high fat diet fractures at the same interval.

The strength of unfractured left fibulae, in the animals with fractured right fibulae, increased to the twelfth day as the primary callus was forming in the opposite fibulae. It fluctuated subsequently and ended on the forty-fifth day at a point lower than that of the unfractured left fibula in animals on standard and on high fat diets. The progressive loss in strength was considered as being due to an attempt to meet the demands of the healing fracture. This may be taken to indicate that the diet was unsatisfactory in any one or more of several ways.

In control rats free from fractures on the same diet for the same period of time, fibular strength first increased and then diminished. On an average, the strength of these control fibulae was less than similar controls on standard and high fat diets.

The body weight of both the control and the fractured animals on the high carbohydrate diet was less than that for similar control and fractured rats on standard and high fat diets. The quantity of food and the caloric intake were, however, somewhat greater.

The possible relation of hexose and glycerophosphates to phosphatase has been briefly considered. The question of the antagonism between phosphatase and the hormone of the parathyroid gland has been considered elsewhere.[13]

ADDENDA

COMPLETE DATA FOR HIGH CARBOHYDRATE DIET

TABLE 1a.—*Correlation Between Fibular Length and Fibular Strength for High Carbohydrate Control Group*

	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
	300	375	225	225	425	380	505	450	380	415
	500	515	375	380	375	365	360	375	610	625
	415	400	350	390	465	525	405	450	755	775
	225	200	425	450	500	430	475	510	435	410
	310	330	260	300	505	460	475	560	670	675
	295	215	245	250	530	490	425	515	...	...
	275	290	240	260	560	640	405	360	...	...
	350	360	505	525	480	475	470	430	...	...
	430	460	365	375	...	...	705	600	...	...
	300	335	310	225	...	...	700	710	...	...
	410	365	260	275	...	...	635	505	...	...
	350	370	225	230	...	...	550	600	...	...
	300	350	360	340	...	...	...	...	...	...
	200	180	310	385	...	...	...	...	...	...
	310	305	310	380	...	...	...	...	...	...
	305	245	395	410	...	...	...	...	...	...
	450	460	390	315	...	...	...	...	...	...
	205	175	...	...	...	...	...	...	...	...
	315	260	...	...	...	...	...	...	...	...
	170	200	...	...	...	...	...	...	...	...
	295	200	...	...	...	...	...	...	...	...
	250	200	...	...	...	...	...	...	...	...
Arithmetic mean	316	309	326	306	491	471	509	505	570	580
Combined arithmetic mean....	313		316		481		507		575	

TABLE 2a.—*Correlation Between Fibular Length and Animal Weight for High Carbohydrate Control Group*

2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.	2.4 Cm.
190	190	202	228	254
190	190	208	235	265
190	198	240	242	275
190	198	243	242	285
190	202	248	256	295
190	205	250	265	...
190	205	255	270	...
194	214	280	272	...
195	216	...	272	...
195	218	...	280	...
195	218	...	282	...
196	225	...	295	...
196	235	...	...	...
197	238	...	...	...
198	240	...	...	...
198	245	...	...	...
200	258	...	...	...
202	...	...	...	...
204	...	...	...	...
205	...	...	...	...
210	...	...	...	...
210	...	...	...	...
196	217	241	261	275

TABLE 3a.—*Correlation Between Animal Weight and Fibular Strength for High Carbohydrate Control Group*

190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
Left	Right	Left	Right	Left	Right	Left	Right
415	400	275	155	380	415	435	410
500	515	360	340	560	640	670	675
300	375	360	375	475	560	550	600
225	225	310	385	390	315	700	710
275	290	310	380	425	515	635	505
225	200	465	525	610	625	...	...
375	380	475	510	405	360	...	...
310	330	405	450	470	430	...	...
295	215	590	430	755	775	...	...
350	360	395	410	...	...	...	...
430	460	505	460	...	...	...	...
300	335	530	490	...	...	...	...
410	365	...	...	...	...	...	...
350	370	...	...	...	...	...	...
300	250	...	...	...	...	...	...
200	180	...	...	...	...	...	...
425	450	...	...	...	...	...	...
350	390	...	...	...	...	...	...
305	245	...	...	...	...	...	...
310	305	...	...	...	...	...	...
450	460	...	...	...	...	...	...
425	380	...	...	...	...	...	...
205	175	...	...	...	...	...	...
260	300	...	...	...	...	...	...
315	260	...	...	...	...	...	...
240	260	...	...	...	...	...	...
245	250	...	...	...	...	...	...
375	365	...	...	...	...	...	...
250	200	...	...	...	...	...	...
295	200	...	...	...	...	...	...
505	525	...	...	...	...	...	...
365	375	...	...	...	...	...	...
310	225	...	...	...	...	...	...
260	275	...	...	...	...	...	...
225	230	...	...	...	...	...	...
325	318	415	409	497	515	598	580
322		412		506		589	

TABLE 4a.—*Force and Ratio for High Carbohydrate Control Group*

Post-operative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To $(10.W)^{2/3}$	Left	Right	Left	Right
6	2730	194	155.6	350	360	225	231
	2731	198	157.7	310	305	197	193
	2732	238	178.3	310	385	174	216
	2733	196	156.6	350	370	224	236
Arithmetic mean with standard deviation		207				205±11	219 ±8
9	2726	190	153.4	415	400	270	261
	2727	270	193.9	405	360	209	186
	2728	205	161.4	245	250	152	155
	2729	190	153.4	500	515	326	336
		214				239±33	235±35
12	2722	295	205.7	550	600	267	292
	2723	272	194.9	470	430	241	221
	2724	265	191.5	425	515	222	269
	2725	190	153.4	300	375	196	244
		256				232±13	257±13
15	2718	250	184.2	530	490	288	266
	2719	295	205.7	670	675	326	328
	2720	242	180.3	405	450	225	250
	2721	282	199.6	635	505	318	253
		267				289±20	274±16
18	2714	255	186.7	560	640	300	343
	2715	280	198.6	700	710	353	358
	2716	190	153.4	225	225	147	147
	2717	195	156.1	430	460	275	296
		230				269±38	286±42
21	2678	242	180.3	475	510	263	283
	2679	202	159.8	425	380	266	238
	2680	235	176.8	360	375	204	212
	2847	198	157.7	305	245	193	155
		219				232±17	222±23
24	2674	214	166.1	505	525	304	316
	2676	200	158.8	450	460	283	290
	2677	208	162.9	375	365	230	224
	2846	210	164.0	250	200	152	122
		208				242±29	238±37
27	2661	196	156.6	300	250	192	160
	2662	204	160.9	315	260	196	162
	2663	195	156.1	300	335	192	215
	2736	210	164.0	295	200	180	122
		201				190± 3	165±17
30	2656	216	167.1	365	375	218	224
	2657	240	179.3	310	380	173	212
	2658	190	153.4	275	290	180	190
	2734	197	157.2	200	180	127	115
		211				175±16	185±21
33	2652	218	168.1	310	225	185	134
	2653	190	153.4	225	200	147	130
	2654	235	176.8	360	340	204	192
	2655	195	156.1	410	365	263	234
		210				200±21	173±22
36	2352	258	188.1	390	315	207	168
	2353	225	171.7	225	230	131	134
	2354	218	168.1	260	275	155	164
	2355	245	181.7	395	410	217	226
		237				178±18	173±17
39	2349	190	153.4	375	380	244	248
	2350	202	159.8	205	175	128	110
	2351	265	191.5	610	625	318	326
	2356	275	196.3	755	775	385	395
		233				269±48	270±53
42	2648	248	183.2	505	460	276	251
	2649	240	179.3	465	525	259	292
	2650	198	157.7	350	390	222	248
	2651	198	157.7	425	450	269	286
		221				257±10	269±10
45	2644	243	180.8	500	430	326	238
	2645	202	159.8	260	300	163	188
	2646	190	153.4	310	330	202	215
	2647	205	161.4	240	260	149	161
		210				210±35	201±14

TABLE 5a.—*Weight and Food for High Carbohydrate Control Group*

Post-operative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
6	2730	200	194	200	99	83
	2731	215	198	210	88	178
	2732	240	238	236	140	110
	2733	222	196	205	87	83
Arithmetic mean.....		219	207	213	104	114
9	2726	190	190	172	86	86
	2727	275	270	273	82	155
	2728	210	205	205	91	143
	2729	190	190	160	98	136
		216	214	203	89	130
12	2722	300	295	310	104	169
	2723	280	272	245	93	163
	2724	265	265	275	105	163
	2725	210	190	190	109	183
		264	256	255	103	170
15	2718	250	250	230	191	239
	2719	295	295	278	93	171
	2720	230	242	248	95	157
	2721	280	282	288	95	176
		264	267	261	119	186
18	2714	260	255	254	102	215
	2715	208	280	265	...	...
	2716	198	190	152	100	231
	2717	210	195	190	100	278
		242	230	215	101	241
21	2678	254	242	223	144	274
	2679	218	202	198	120	355
	2680	248	235	232	120	319
	2847	190	198	152	128	190
		228	219	201	128	285
24	2674	224	214	210	80	277
	2676	202	200	171	119	298
	2677	214	208	202	131	330
	2846	195	210	196	92	277
		209	208	195	106	296
27	2661	195	196	150	43	308
	2662	232	204	193	42	312
	2663	212	195	176	48	279
	2736	225	210	190	58	322
		216	201	177	48	305
30	2656	240	216	147	59	303
	2657	250	240	166	100	346
	2658	195	190	147	64	351
	2734	200	197	171	76	246
		221	211	158	75	312
33	2652	230	218	218	86	433
	2653	198	190	173	35	374
	2654	262	235	192	42	297
	2655	220	195	190	52	363
		228	210	193	54	367
36	2352	250	258	206	98	297
	2353	212	225	144	108	335
	2354	222	218	190	104	311
	2355	238	245	200	102	315
		231	237	185	103	315
39	2349	190	190	148	85	280
	2350	200	202	150	95	313
	2351	262	265	190	120	391
	2356	270	275	198	118	342
		231	233	172	105	332

TABLE 5a.—*Weight and Food for High Carbohydrate Control Group—Continued*

Post-operative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
42	2648	248	248	146	70	410
	2649	258	240	164	71	512
	2650	210	198	160	60	468
	2651	200	198	160	84	391
		229	221	158	71	445
45	2644	250	243	140	62	435
	2645	215	202	138	86	425
	2646	200	190	163	52	447
	2647	230	205	145	45	407
		224	210	147	61	429

TABLE 7a.—*Force and Ratio for High Carbohydrate Diet Fractured Group*

Post-operative Days	Rat Number	Weight (W)		Force (F)		Ratio (R)	
		At Operation	To $(10.W)^{2/3}$	Left	Right	Left	Right
6	2059	270	193.9	365	0	188	0
	2060	223	170.7	385	0	226	0
	2061	227	172.7	340	95	196	55
	2062	240	179.3	335	0	187	0
	2063	265	191.5	375	15	196	7
Arithmetic mean with standard deviation mean						199±6	12±10
9	2052	275	196.3	480	105	245	54
	2055	200	158.8	290	170	183	108
	3328	232	175.2	425	45	243	26
	3329	220	169.1	605	190	358	116
						208±32	76±19
12	2042	245	181.7	250	130	138	72
	2043	272	194.9	550	255	282	131
	2044	258	188.1	480	160	255	85
	2045	276	196.8	625	265	318	135
	2048	190	153.4	340	135	222	88
						243±28	102±12
15	2036	198	157.7	230	95	146	60
	2037	190	153.4	375	85	244	55
	2041	245	181.7	265	140	146	77
	3118	194	155.6	350	265	225	170
	3119	190	153.4	220	240	144	157
	3117	190	153.4	290	185	189	121
						182±17	107±19
18	2031	250	184.2	240	150	130	81
	2032	198	157.7	220	140	139	89
	2034	285	201.0	430	240	214	119
	2670	270	193.9	630	180	325	93
	2671	190	153.4	300	185	196	121
						201±32	101± 7
21	3335	252	185.2	525	185	283	100
	3332	190	153.4	375	240	244	156
	3331	190	153.4	340	150	221	98
	3333	220	169.1	580	140	343	83
	3334	240	179.3	555	190	310	106
						278±19	108±16
24	2011	194	155.6	275	185	177	119
	2066	280	198.6	560	350	282	176
	2660	260	189.1	405	220	214	116
	2667	272	194.9	395	90	203	46
	2672	228	173.2	560	90	323	52
						240±24	102±22
27	1999	190	153.4	320	205	209	134
	2002	265	191.5	405	170	211	89
	2003	272	194.9	525	360	269	185
	2005	254	186.2	275	105	148	56
	2067	250	184.2	370	360	201	195
						208±17	132±24

TABLE 7a.—*Force and Ratio for High Carbohydrate Diet Fractured Group —Continued*

Post-operative Days	Rat Number	Weight (W) At Operation	Weight (W) To $(10.W)^{2/3}$	Force (F) Left	Force (F) Right	Ratio (R) Left	Ratio (R) Right
30	2013	255	186.7	390	345	209	184
	2015	280	198.6	350	190	177	96
	2016	200	158.8	280	275	176	173
	2018	205	161.4	250	225	155	139
	2850	285	201.0	400	325	199	162
						183± 9	151±14
33	1982	252	185.2	390	335	211	181
	1985	202	159.8	360	200	225	125
	1987	200	158.8	...	255	...	161
	2665	213	165.6	530	235	320	142
	2852	192	154.4	225	170	146	110
	2851	260	189.1	390	250	206	132
						222±26	142±11
36	1980	222	170.2	310	130	182	76
	1981	190	153.4	270	210	176	137
	1983	255	186.7	250	205	134	110
	1986	275	196.3	440	320	224	163
	2853	232	175.2	275	155	157	88
						175±13	115±14
39	1993	206	206.2	300	240	145	117
	1995	198	157.7	220	80	139	51
	1996	262	190.1	350	160	184	84
	1997	200	158.8	230	275	145	173
	1998	260	189.1	325	175	172	93
						157± 8	103±19
42	1968	210	164.0	200	190	122	116
	1969	212	165.0	315	240	191	146
	1970	220	169.1	510	380	302	225
	1971	200	158.8	180	160	113	101
	1972	225	171.7	360	245	209	143
						188±29	146±19
45	1962	209	163.5	225	190	138	116
	1963	238	178.3	175	200	98	112
	1965	228	173.2	200	195	115	113
	1966	248	183.2	415	450	227	246
	1967	252	185.2	410	255	221	138
						160±25	145±23

TABLE 8a.—*Weight and Food for High Carbohydrate Fracture Group*

Post-operative Days	Rat Number	Weight Start	Weight Operation	Weight Death	Food Consumed Start to Operation	Food Consumed Operation to Death
6	2059	274	270	258	110	119
	2060	228	223	220	101	94
	2061	219	227	232	87	100
	2062	245	240	238	117	87
	2063	292	265	282	116	143
Arithmetic mean.....		252	245	246	106	109
9	2052	268	275	280	179	176
	2055	200	200	195	78	107
	3328	220	232	220	90	102
	3329	205	220	205	105	112
		223	232	225	113	124
12	2042	230	245	222	112	154
	2043	278	272	268	143	222
	2044	262	258	256	118	199
	2045	280	276	290	102	185
	2048	190	190	195	110	162
	2065	266	255	263	114	178
		251	249	249	118	183

TABLE 8a.—*Weight and Food for High Carbohydrate Fracture Group—Continued*

Post-operative Days	Rat Number	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
15	2036	198	198	205	98	137
	2037	190	190	192	105	179
	2041	245	245	240	113	194
	3118	200	194	165	88	158
	3119	190	190	164	70	122
	3117	190	190	150	82	117
		202	201	186	93	151
18	2031	245	250	238	119	191
	2032	198	198	188	110	224
	2033	238	190	172	80	185
	2034	285	285	275	90	214
	2670	268	270	255	102	315
	2671	202	190	175	58	197
		239	231	217	93	221
21	3331	190	190	154	90	252
	3332	195	190	165	68	200
	3333	232	220	205	92	257
	3334	255	240	218	95	270
	3335	260	252	186	98	253
		226	218	232	89	246
24	2011	195	194	195	75	218
	2066	300	280	295	110	335
	2660	255	260	193	...	219
	2667	280	272	248	...	...
	2672	218	228	172	95	245
		250	247	221	93	254
27	1999	196	190	192	84	373
	2002	272	265	235	116	320
	2003	280	272	230	125	291
	2005	262	254	230	161	509
	2067	245	250	230	125	310
		251	246	223	122	361
30	2031	240	255	248	153	420
	2015	254	280	230	88	378
	2850	288	285	248	182	430
	2016	195	200	195	73	321
	2018	216	205	220	81	312
		239	245	228	115	372
33	2852	190	192	173	...	367
	1982	290	252	262	100	434
	1985	225	202	200	...	...
	1987	198	200	195	60	294
	2665	242	213	180	62	392
	2851	245	260	225	126	394
		232	220	206	87	376
36	2853	220	232	215	54	374
	1980	220	222	198	100	368
	1981	200	190	180	100	382
	1983	280	255	180	60	382
	1986	295	275	215	90	393
		243	235	198	81	380
39	1993	300	296	270	108	397
	1995	205	198	180	91	330
	1996	276	262	205	100	402
	1997	215	200	180	96	463
	1998	258	260	205	90	501
		251	243	208	97	419
42	1968	208	210	177	98	430
	1969	220	212	205	97	564
	1970	210	220	240	101	593
	1971	208	200	183	96	398
	1972	234	225	206	83	512
		216	213	202	95	499
45	1962	232	209	180	102	619
	1963	251	238	177	92	540
	1965	220	228	202	109	570
	1966	242	248	242	116	709
	1967	252	252	243	98	608
		239	235	209	103	609

ETIOLOGY OF FEMORAL HERNIA

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Are femoral hernial sacs of congenital or acquired origin? The answer to this question should be of interest to students of anatomy and embryology and to biologists in general, and of even greater interest and real practical importance to surgeons. If these sacs are always congenital, then simple extirpation of the peritoneal diverticulum would hold out promise of cure to patients afflicted with this condition. If, on the other hand, all are acquired, then removal of the sac alone will not be sufficient, and other factors concerned in the process must be corrected before a lasting repair can be obtained.

In order to study the factors that may have a bearing on this problem, two different types of observations were made. The first consisted of clinical material, that is, all femoral hernias seen at the University Hospital; the second, of anatomic dissections and measurements.

All femoral hernias, with the exception of a rare type that passes directly through the lacunar ligament (Gimbernat's), go through the lacuna vasorum. The latter (fig. 1) is an almost oval space lying under Poupart's ligament and separated from the lacuna musculorum by a strip of fascia, the iliopectineal ligament. The lacuna vasorum is bounded anteriorly by Poupart's ligament, posteriorly by the pubis covered by the pectineous muscle and Cooper's ligament, internally by Gimbernat's ligament and externally by the iliopsoas muscle covered by the iliopectineal ligament. The structures that pass through the lacuna vasorum are the femoral artery and vein, the crural branch of the genitocrural nerve and the femoral canal. The femoral ring lies between the femoral vein and Gimbernat's ligament. It is separated from the peritoneal cavity by the septum crurale. The femoral canal contains a few lymphatic vessels, some fat and frequently a lymph gland known as Rosenmueller's gland.

Accurate measurements of the femoral ring itself are impossible because of its variable lateral wall consisting of the easily collapsable femoral vein. Panton has been the only one to attempt to measure

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Abridgment of thesis submitted to the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery (Minor Anatomy), March 20, 1930.

accurately the lacuna vasorum. Practically no reports have been made on the size of any of its contents, the femoral vein and artery or of its anterior boundary or Poupart's ligament. In this study all of these structures were considered in relation to crown-heel length, age, sex and side concerned.

THEORIES CONCERNING THE ETIOLOGY OF FEMORAL HERNIA

Mechanical Theory.—An old theory, known as the mechanical, in which abnormal length of the attaching membranes of the intestines was believed to be the main etiologic factor plus weakness of the

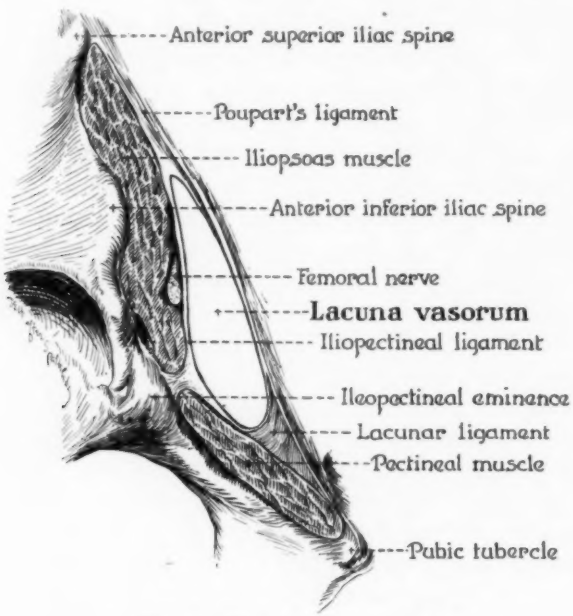

Fig. 1.—The lacuna vasorum.

abdominal parietes has few, if any, champions at present. Measurements made by Callender, Lockwood and Robinson showed that practically all mesenteries were long enough to reach well below the inguinal and femoral rings, and that persons with hernia failed to show any abnormality in the length of their mesenteries.

Pressure Theory.—Sir Arthur Keith (1906) said: "Most of us believe that two conditions are necessary for the production of a hernia: (1) a single or repeated sudden rise in intra-abdominal pressure; (2) a weak spot in the abdominal wall." He believed that the subperitoneal tissue in the femoral region was lax, and that the movable peritoneum was forced into a defect, the femoral ring, by one or more repeated

forces arising intra-abdominally. He also stressed the effect of exercise, coughing and straining on the expansion of the femoral vein above its valves acting as a water hammer and thereby increasing the size of the defect already present, thus allowing the protrusion of a diverticulum of peritoneum.

Hare agreed with Keith and believed that the upright position assumed by man increases the intra-abdominal pressure, as do heavy occupations, coughing, dyspnea, etc., while age and obesity, paralysis and emaciation weaken the supporting walls.

Along the same line, Battle stated: "The original cause of the hernia (femoral hernia) is not the formation of a peritoneal pouch, that is secondary to other things." Pilcher believed that in the aged there is a gradual relaxation of the structures forming the femoral canal. He felt, however, that femoral hernias are of congenital origin in children. Harvey stated that femoral hernias are never of congenital origin. Haynes concluded that the presence of a large easily compressible vein near a distinctly weak spot in the abdominal wall is an important factor, especially as the vein leaves the cavity in a straight line and not obliquely as does the spermatic cord through the inguinal canal. He thought that the only reason there were so few femoral hernias is that this weak area fortunately is small in extent in most cases.

Denny considered pregnancy a predisposing cause, since he considered that the fascia was weakened and the opening enlarged as a result of the strain accompanying labor. He further stated that the intestine itself passes through a patulous ring forming its own canal by pressing forward those parts in front of it that have the least resistance.

Traction Theory.—(*a*) Congenital or Preformed Sac Theory: Since 1902, Russell of Australia has been the chief defender of the saccular theory in regard to the causation of femoral hernia. Much the same idea was put forth by Jaboulay as early as 1899, and Dussac in 1900. Russell believed that the sac is formed prior to the development of the hernia, but that it need not be present at birth. According to him, during the second month of fetal life at the time the limb-buds and pleuroperitoneal cavity are forming, the blood vessels are also being developed, including those to the future limbs. It is possible, he believed, that at this time a small pouch of peritoneum from the embryonal pleuroperitoneal cavity may be involved in this growth process and attach itself to the femoral artery. Later, as the blood vessels develop and push down the extremity, this pouch of peritoneum is also pulled down with them through the ring. The sac is never discovered at birth,

because the diverticulum is too small at this time, but later as the limb grows the blood vessels lengthen and carry along this attachment of peritoneum. This theory is the only one, he felt, that could explain why a femoral hernia sac after leaving the saphenous opening takes its usual upward course. Russell's idea is that this is accomplished by the pull of one or more of the branches of the femoral artery. The loculated sacs described by Macready and Middleton are used to substantiate this theory further. Each loculus is thought to follow one of the three main branches of the femoral artery: the superficial circumflex iliac artery, the superficial epigastric artery and the superficial external pudenal. The type of femoral hernia that goes down the thigh follows the main femoral vessels.

Russell carried this theory into practical use surgically, and does not believe that it is necessary to do more than remove the femoral sac and leave the ring entirely unaltered. Keith believed, however, that Russell effectually plugged the canal by leaving a wad of peritoneum after twisting and ligating the sac.

Middleton, LaRoque, Coley, Watson, Erdmann, Horsley, Lang and Panton concur with Russell's ideas.

The arguments against the foregoing theory are many. At no stage in the development of the fetus up to the time of birth has any one demonstrated such a diverticulum. Sir Arthur Keith (1928) dissected over 500 bodies without ever seeing one. Dr. Scammon (1930) similarly examined 300 and never noted this condition. In over 100 bodies that I dissected with this point in view, there was no suggestion of its occurrence in a single instance. The case of a femoral hernia in a 3 months old fetus reported by Cushier in 1892 can hardly be considered as approaching in any way the character of the ordinary femoral hernia. In her case the integument had been broken through, and the intestines were lying out on the thigh. There were also other gross defects present. She reported that Picquet in 1846 had a case almost similar. In his case the liver and the intestine protruded through the ring although the skin was still intact.

Studies on the growth of blood vessels seem to indicate that they do not grow with the limb by extending outward, but that lineal growth of blood vessels is closely correlated with the lineal growth of adjacent tissues (Scammon, Schwalbe). Vessels do not recede further from the trunk with growth; if they did, the recurrent vessels so numerous in the four extremities would be pulled away from their destinations instead of toward them.

The change of the course upward of femoral hernia is explained by Haynes by two factors: (1) the cribriform fascia is more firmly attached at its lower than at its upper margin; (2) the superficial veins,

the pubic, the epigastric and the circumflex iliac, empty into the saphenous vein before it enters the femoral vein, and consequently these vessels would have to be stretched or displaced in order to allow the hernia to go downward.

As to the loculated sacs, the femoral region is by no means the only place they occur. Bevan described them in the inguinal region. McQueeney found 9 cases of multiple sacs in 129 hernias of various types. In 1900, Moynihan reported a large number of properitoneal and interstitial hernia, which were all bilocular. It would be difficult to attribute any of these to the effect of growth of blood vessels.

(*b*) Theory of Gubernacular Pull: Murray also believed that the femoral hernial sac is preformed but thought that the gubernaculum is responsible for its presence. Although there is no proof that the gubernaculum is in any way responsible for the descent of the testicle into the scrotum or for the formation of the processus vaginalis, he used this as the basis of his ideas. He believed that abnormal bands of this tissue often end elsewhere than in the scrotum, and that usually these abnormal bands are slender. Occasionally, however, a larger abnormal crural band is formed which, because of its function of pulling on the peritoneum, produces a diverticulum in the region of the crural ring, and with the growth of the individual a larger and true hernial sac is formed. He thought that this is the explanation for Ferguson's and Fauntleroy's cases of cruroscrotal hernia. To substantiate this hypothesis, he had the fundus of a femoral hernial sac examined microscopically and found striated muscle fibers present. Piersol described the gubernaculum testis to be made up of smooth muscle fibers and connective tissue, except its lowest portion which is made up of striated muscle derived from the muscles of the abdominal wall. After birth the gubernaculum becomes almost entirely atrophic and gives little if any evidence of muscle content. If this was the cause of femoral hernia, it seems strange that women show such a preponderance of femoral hernia over men, even though similar but much smaller and more slender bands are present in the former.

(*c*) Theory of Traction by Fat: Paré probably was the first to describe fatty hernia and to regard fat as a likely cause of intestinal hernia. Littré also described fatty hernia, or hernia adiposa. Since then many similar cases have been described. These hernias arise in the properitoneal fat and find their way through the femoral canal and out through the saphenous opening. Many are made up entirely of fat; many others have in their centers small diverticula of peritoneum. Even the largest of femoral hernial sacs has, as a general rule, a thick covering of fat surrounding them, especially at the fundus. Annandale, in 1869,

quoted Quain, who believed that the protrusion of the fatty mass was the first condition present in the formation of a hernia, a process or tube of peritoneum being gradually drawn down into it secondarily. Haas, in 1896, stated that he believed that the fat found at the lowest part of the sac was the causative factor in the development of this form of hernia, and that the fat first dilated the ring and then dragged along a pouch of peritoneum with it. The fat was probably forced along by muscular action and not, he thought, by reason of its weight alone.

Buckley called this same process "the acquired saccular theory." According to him, there is a weakness of the abdominal wall, and in the case of the femoral hernia this is present at the crural ring. There is also an accumulation of loose properitoneal fat with adhesions from it to the peritoneum and also to the fat that plugs the crural canal. The peritoneum is loose and can be easily stretched. Increased intra-

TABLE 1.—*Frequency of the More Common Types of Hernia*

Author	Year	Total Number of Hernia	Inguinal	Femoral	Others
Parker	1893	190	137	25	28
Stinson	1896	97	79	5	13
Pott	1903	15,028	14,095	933	..
Morison	1904	95	75	10	10
Hilgenreiner	1904	891	651	119	21
De Garmo	1905	1,250	1,140	110	..
Bull and Coley	1905	53,686	50,961	2,725	..
Pfister	1906	300	234	35	31
Stephens	1926	2,090 (men)	2,051	39	..
McQueeney	1926	129	95	8	26
		73,756	70,115	4,009	129

abdominal pressure forces the fat into the canal and then out under Poupart's ligament and with it the properitoneal fat. The latter, then, in many cases carries with it a diverticulum of peritoneal. This process is probably a very slow one. After a pouch is formed it may later become further distended because of the presence of abdominal contents within it. Pressure atrophy tends to thin out the fat surrounding large femoral hernial sacs.

Keith (1906) believed it is possible for the fat, because of its semi-fluid nature, to act as a water hammer and force its way under Poupart's ligament carrying with it the peritoneum, and that this same process accounts for the herniation of properitoneal fat seen in the linea alba. Here also the vessels pass through vascular foramina.

Lutz, Keyes, Souttar, Friedman, Parker, McQueeney and Roeder favor this explanation.

CLINICAL STUDY

Incidence.—From 1909 to 1928, inclusive, there were seen at the University Hospital 52 patients with femoral hernia. Forty-five of these

were treated surgically and 7 were not. In the latter group a few refused operation, and in others some disability was present which contraindicated surgical treatment. During this same period there were 1,130 patients with inguinal hernia, or a proportion of 21 inguinal to 1 femoral.

Table 1 shows the figures given by various authors as to the frequency of the various types of the more common hernia. From these figures, the proportion of inguinal hernia to femoral is found to be 17 : 1.

Sex Distribution.—There were 16 males and 36 females in this series, or a proportion of 1 male to 2.2 females.

Table 2 shows the figures as to sex distribution collected from other authors. The proportion of males to females is 1 : 2.3. Coley, in 1906, found the proportion to be 1 : 6 in adults and 1 : 2 in children.

TABLE 2.—*Sex Distribution in Femoral Hernia*

Author	Year	Total Number of Cases	Males	Females
Bull and Coley	1898	1,927	558	1,369
Hilgenreiner	1904	119	13	106
De Garmo	1905	99	16	83
Pfister	1906	35	7	28
Battle	1908	81	14	67
Bachelor	1909	15	5	10
Groves	1923	22	1	21
Harvey	1924	52	28	24
Herzfeld	1924	4	1	3
Coley	1924	101	43	58
Rutherford	1927	5	1	4
Totals		2,460	687	1,773

Keith (1925) concluded from collected figures that out of every 1,000 ruptured males, 970 would have inguinal, 20 femoral and 10 umbilical hernia; while out of 1,000 ruptured females, 500 would have inguinal, 340 femoral and 160 umbilical hernia. Berger stated that 37.1 per cent of all hernia in females are femoral, while only 6.6 per cent are femoral in males.

Age Incidence.—The peak age incidence for this condition begins at the age of 25 and ends at 45 (fig. 2). During this period of twenty years occur 44 per cent of all cases. Berger found the peak in females to begin at 45 and end at 80, with the maximum point at 70 years of age. De Garmo (1905) found the peak somewhat earlier in life, from 20 to 50 years.

Femoral hernias are rare in children. Sabourin reported a case in a premature infant. The youngest patient in our series was 6 years of age. There was one other child under 10. Bull and Coley reported 69 of 2,179 cases of femoral hernia to be in children under 14, but only 13 of those were under 10 years of age. The youngest patient in their series was 2 years old. Wernher reported 7 children under 5.

Hilgenreiner reported 3 of 119 patients to be under 20; Harvey, 1 child in 52 cases, and Stiles only 1 in 360 cases. MacLennan found only 6 femoral hernias in children to 1,000 inguinal. Murray, in 1910, collected the records of 104 cases of femoral hernia in children under 15 years of age.

Macready gives the following statistics as to the age incidence for children under 20: Of 134 males, there were 7 from 1 to 5 years of age, 19 from 6 to 10, 29 from 11 to 15 and 29 from 16 to 20; of 338 females, there were 8 from 1 to 5, 22 from 6 to 10, 50 from 11 to 15 and 258 from 16 to 20 years of age.

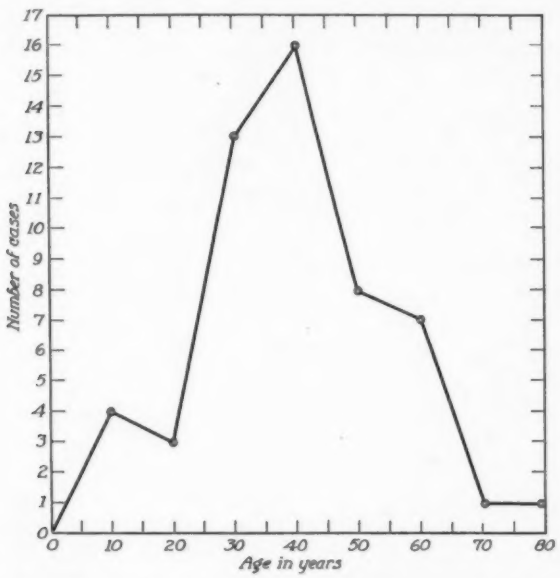

Fig. 2.—The incidence of femoral hernia according to age.

Distribution of Femoral Hernia as to Side.—In our series of cases, 33 hernias developed on the right side, 18 on the left and in 2 cases they were bilateral. Sixty-three per cent were right-sided.

Table 3 shows that 60 per cent of femoral hernias are on the right side.

Bigg found that in 100 femoral hernias in women 52 were on the right side, 40 on the left and 8 were bilateral; while in men, 50 were on the right side, 33 on the left and 17 were bilateral.

Piersol stated:

The almost invariable preponderance of right-sided hernia in all varieties, at all ages, in both sexes has been variously attributed to (*a*) the greater bulk and

weight of the liver; (*b*) to right-sidedness in walking and lying, and to the greater strain on the muscles of the right side caused by "right-handedness"; (*c*) to the inclination from left to right of the mesentery of the small intestine as it descends; (*d*) to the greater frequency of incomplete descent of the testes and of a patulous funicular process on the right side; and (*e*) to the larger capacity and circumference of the right side of the pelvis (Knox, Macready) as compared with the left, causing a corresponding increase in the size of the right femoral ring.

The Effect of Pregnancy on the Occurrence of Femoral Hernia.—There were 36 females in the series from the University Hospital. In two of these no mention was made of whether or not the patient had children. Eight females (which includes 3 children) had had no pregnancies. Four women had only a child each, while 24 had more, with an average number of 6.4 children for each woman.

Kingdon found that in 138 single women who were ruptured 68 had inguinal and 70 femoral hernia; in 32 married but childless women

TABLE 3.—*Distribution of Femoral Hernia as to Side*

Author	Year	Total Number of Cases	Right	Left	Bilateral
De Garmo	1905	99	59	29	11
Battle	1908	81	43	38	..
Harvey	1924	52	37	15	..
Totals		232	139	82	11

15 had inguinal and 17 femoral hernia, while in 511 mothers 313 had femoral and only 198 inguinal hernia.

Birkett found that in 193 ruptured females under 15 years of age 184 had inguinal hernia and 9 femoral; in 111 single women 50 had inguinal hernia and 62 femoral, while in 440 mothers 178 had inguinal and 262 femoral hernia.

Macready found that the number of single women as compared to the married and widowed between the ages of 20 and 45 was 1 : 1.6, and that the ratio of women who have borne children to those who have not was 1.2 : 1. In ruptured females the childless are to the mothers as 1 : 2.7.

Contents of the Femoral Sac.—In 20 cases in the University Hospital series the contents of the sac were not recorded. In 7 instances no operation was performed. In the remaining cases, 12 sacs were entirely empty, 6 contained normal omentum, 6 strangulated omentum and 4 strangulated bowel. In no case was normal bowel found. About 20 per cent of the patients, then, were operated on primarily because of strangulation. Morton operated on 27 of 47 patients for this reason and Bachelor on 52 of 182.

Murphy reported Fantino's findings in 4,200 cases of hernia, in which 6.54 per cent of the inguinal hernias and 38 per cent of the femoral were strangulated.

Table 4 shows that more than 40 per cent of all strangulated hernia are femoral, while only 5 per cent of all hernia belong to this type. Femoral hernias, then, are eight times more liable to become strangulated than inguinal.

Recurrences Following Operation for Femoral Hernia.—Of the 52 patients admitted to the University Hospital with femoral hernia, 6 gave a history of having had a previous operation for the same condition.

Keynes stated that at the City of London Truss Society, over a ten year period, 350 patients were seen with recurrences and that of these

TABLE 4.—*Strangulated Hernia*

Author	Year	Total Number of Cases	Inguinal	Femoral	Others
Parker	1893	61	30	21	10
Thorburn	1903	110	55	37	18
Hilgenreiner	1904	362	208	134	20
Erdmann	1904	58	31	19	8
Hilton	1907	529	250	250	29
Alexander	1913	105	60	25	20
Totals		1,225	634	486	105

TABLE 5.—*Recurrences Following Operations for Femoral Hernia*

Author	Year	Total Number of Cases	Recurrences
De Garmo	1905	99	3 (not all traced)
Bachelor	1909	103	1
Coley and Hoguet	1918	99	14
Groves	1923	21	0
Coley	1924	28	3
Harvey	1924	46	0
Stephens	1926	39	4

275 were inguinal and 90 femoral hernias. As 17 inguinal hernias are found to 1 femoral, one may conclude that femoral hernias are several times (4:5) more liable to recurrence than inguinal.

In order to determine, if possible, the number of recurrences following the operations for femoral hernia performed at the University Hospital, questionnaires were sent to each of these patients.

Out of the 45 letters sent out, 20 were returned unopened.[1] Of the 25 people who answered, 23 were entirely free from recurrence while in 2 there was definite evidence of a return of their former trouble. Both of these patients were unable to come back to the hospital for an examination.

1. The transient residence of the class of patient admitted to the University of Minnesota Hospital makes an adequate follow-up very unsatisfactory.

Statistics on the number of recurrences following operation for femoral hernia are relatively few.

Watson collected the figures from various clinics and in 1,444 cases found recurrence present in less than 5 per cent.

In 182 in which a muscle plastic operation was done, there were 9.89 per cent recurrences.

Noble said that a fair estimate for recurrence in inguinal hernia is from 3 to 5 per cent, while for femoral hernia it is from 25 to 30 per cent.

For many years there has existed a controversy as to whether or not it is necessary for the femoral canal to be closed after the sac is removed to obtain a cure. Pott found that in those cases in which the sac only was removed for the repair of femoral hernia, there were 63.3 per cent cures, while in those cases in which the sac was ligated and the ring closed, the cures were 76.4 per cent. Bull, in 1890, treated 13 patients by simple ligation of the sac, and one year later he was able to trace 8 with 3 recurrences. Bresset studied 395 femoral hernias, and in 232 cases without closure of the ring found 29 per cent recurrence, while in 163 with closure of the ring recurrence took place in only 8.6 per cent. Keynes, quoting the work of Professor Gask, stated that the latter in order to test the point as to whether or not it was necessary to close the ring to obtain a cure in femoral hernia merely removed the sac in 10 cases through a laparotomy incision. He found 6 prompt recurrences. However, Russell, LaRoque, the late Ochsner and others claim excellent results by simply removing the sac from below.

ANATOMIC STUDIES

Very few measurements have been made of the structures concerned in the formation of femoral hernia. Books on anatomy and surgery with few exceptions and without any apparent proof state that femoral hernia are found more often in females than in males because the femoral ring is larger in the former. To measure accurately the femoral ring is impossible because of its variable lateral wall, the femoral vein. The best indirect method to secure this information was to measure the lacuna vasorum and the vessels, then by subtracting the sum of the diameters of the vessels from the cross-section area of the lacuna one could determine the approximate size of the ring, or the amount of space available for the development of a femoral hernia. Panton, in 1922, first showed that the distance from the anterior superior spine of the ilium to the pubic spine (Poupart's ligament) was smaller in females than males. He also made linear measurements of the lacuna vasorum and concluded that this structure was larger in females than in males.

In this study the lacuna vasorum was measured by accurately cutting and fitting into its ligamentous borders a piece of celluloid and then determining the surface area of this form by means of a planimeter. The length of Poupart's ligament was taken to be the distance from the anterior superior iliac spine to the pubic tubercle measured with pointed calipers. The caliber of the vessels was determined by using accurately calibrated cones (fig. 3). The thickness of the vessel walls was obtained by the use of an ordinary beam-caliper with a vernier attachment allowing readings to be made to 0.1 mm.

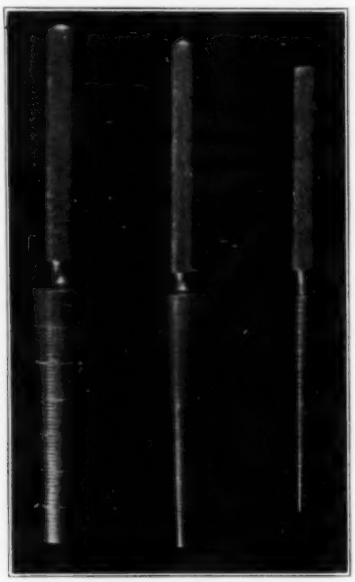

Fig. 3.—Calibrated cones used in the measurement of the diameter of the femoral vessels.

Fresh autopsy specimens only were used. Grossly pathologic pelves were eliminated; otherwise the material was unselected.

Thirty female and 34 male premature and new-born infants, 8 children of various ages, 30 women and 30 men were examined and measured. Height and age were correctly recorded. All hernial sacs in the femoral and inguinal regions were noted.

TREATMENT OF DATA

In order to ascertain more fully the significance of the data collected, it was necessary to apply to it both graphical and numerical analytic methods. The data was first arranged into five tables (tables 6, 7, 8, 9 and 10).

TABLE 6.—*Measurements of the Lacuna Vasorum and Associated Structures in Thirty-Four Male Premature and New-Born Infants*

	Right Side				Left Side				Processus Vaginalis			
C-H Length, Cm.	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber of Vein, Mm.	Caliber of Artery, Mm.	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber of Vein, Mm.	Caliber of Artery, Mm.	Both Open	Right Open	Left Open	Both Closed
34	18	2.3	1.7	1.0	17	2.3	1.6	1.0	+	—	—	—
36	22	2.3	1.7	1.0	25	2.3	1.7	1.0	+	—	—	—
37	28	2.3	1.8	1.0	32	2.3	1.7	1.0	+	—	—	—
38	37	3.1	...	...	34	3.1	...	...	+	—	—	—
39	28	2.8	1.6	1.1	32	2.9	1.7	1.2	—	+	—	—
39	30	3.1	2.9	1.0	32	3.1	3.2	1.1	+	—	—	—
40	55	2.8	1.7	1.1	43	2.6	1.9	1.3	+	—	—	—
40	26	2.9	1.9	1.0	24	2.9	2.1	1.1	+	—	—	—
40	31	3.0	2.2	1.2	28	3.0	2.3	1.2	+	—	—	—
41	26	3.2	1.7	1.0	31	3.2	1.6	1.0	+	—	—	—
41	28	2.7	2.1	1.1	30	2.7	2.2	1.0	+	—	—	—
41	28	2.8	1.6	1.0	27	2.8	1.7	1.0	+	—	—	—
42	28	2.9	1.6	1.1	35	2.8	1.7	1.1	+	—	—	—
42	31	3.7	1.2	1.1	30	3.7	1.7	1.1	+	—	—	—
43	35	3.6	2.7	1.0	33	3.6	2.8	1.0	+	—	—	—
44	46	3.3	2.0	1.2	47	3.4	1.9	1.3	+	—	—	—
45	62	3.6	2.4	1.1	54	3.5	2.5	1.1	+	—	—	—
46	40	3.5	2.4	1.2	42	3.4	2.7	1.2	+	—	—	—
46	35	3.0	3.8	1.5	34	3.0	3.4	1.4	+	—	—	—
48	50	3.6	1.8	1.1	39	3.6	2.0	1.1	+	—	—	—
48	52	3.7	2.7	1.2	46	3.7	2.8	1.2	+	—	—	—
49	40	3.7	1.8	1.4	50	3.8	1.7	1.3	+	—	—	—
50	40	3.3	2.1	1.2	50	3.4	2.0	1.2	+	—	—	—
50	36	4.2	2.2	1.2	35	4.1	2.2	1.2	+	—	—	—
52	66	4.1	2.4	1.4	56	4.2	2.9	1.6	—	—	—	+
52	55	4.0	2.6	1.9	50	3.9	2.9	1.9	—	—	—	+
52	44	3.2	2.0	1.1	45	3.1	1.9	1.1	—	—	—	+
52	41	4.6	2.8	1.2	38	4.6	2.9	1.2	—	—	—	+
52	40	3.6	2.6	1.1	41	3.5	2.2	1.1	—	—	—	+
52	64	4.0	5.0	1.5	57	4.1	4.8	1.4	—	—	—	+
52	46	4.0	3.0	1.4	39	3.9	3.2	1.5	—	—	—	+
53	61	3.8	2.8	1.1	62	3.8	2.6	1.1	—	—	—	+
53	46	4.0	1.6	1.3	60	3.9	2.8	1.3	—	—	—	+
53	67	4.1	3.7	1.7	57	4.2	3.9	1.7	—	—	—	+
Average—									Total—			
45.3	40.6	3.38	2.31	1.18	39.6	3.37	2.39	1.20	18	7	1	8

TABLE 7.—*Measurements of the Lacuna Vasorum and Associated Structures in Thirty Female Premature and New-Born Infants*

	Right Side				Left Side				Processus Vaginalis			
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35	32	2.3	1.6	1.0	31	2.3	1.6	1.0	—	—	—	+
37	23	2.7	1.4	1.0	22	2.6	1.3	1.0	—	—	—	+
38	37	2.4	1.5	1.1	30	2.4	1.6	1.1	—	—	—	+
38	22	2.6	1.8	1.0	23	2.8	1.8	1.0	—	—	—	+
38	23	3.3	2.8	1.2	24	3.3	2.8	1.2	—	—	—	+
39	35	2.8	1.7	1.1	32	2.6	1.9	1.3	—	—	—	+
39	23	2.9	1.6	1.0	26	2.9	1.5	1.0	+	—	—	—
39	29	2.9	2.3	1.0	23	2.9	2.2	1.0	—	—	—	+
41	28	3.0	1.7	1.0	30	2.9	1.8	1.0	—	—	—	+
42	32	2.8	2.6	1.4	30	2.8	2.8	1.0	—	—	—	+
43	32	3.1	2.2	1.1	26	3.1	1.9	1.1	—	—	—	+
43	39	3.0	1.6	1.0	38	2.9	2.7	1.1	—	—	—	+
43	27	3.0	2.4	1.3	30	2.8	2.4	1.4	—	—	—	+
44	50	2.8	...	...	55	2.9	...	...	—	—	—	+
44	42	3.3	2.6	1.4	44	3.3	2.5	1.4	—	—	—	+
44	46	3.5	2.7	1.2	45	3.6	2.6	1.2	—	—	—	+
46	30	3.0	2.2	1.4	29	3.1	2.3	1.3	—	—	—	+
46	45	3.7	2.0	1.1	41	3.7	1.9	1.2	—	—	—	+
48	36	3.6	1.8	1.1	43	3.5	1.6	1.1	—	—	—	+
48	40	3.7	3.2	1.3	32	3.7	3.4	1.3	—	—	—	+
48	32	3.5	2.7	1.3	36	3.5	2.6	1.2	—	—	—	+
49	50	3.5	1.8	1.3	56	3.6	1.9	1.3	—	—	—	+
49	28	3.3	2.9	1.2	29	3.3	2.7	1.1	—	—	—	+
52	77	3.9	2.6	1.2	65	3.9	2.4	1.4	—	—	—	+
52	38	3.3	1.5	1.1	40	3.5	1.8	1.1	—	—	—	+
52	41	3.3	2.3	1.1	42	3.3	2.2	1.2	—	+	—	—
53	60	4.2	2.2	1.7	48	3.9	2.4	1.9	—	—	—	+
54	52	4.0	2.8	1.8	46	4.0	2.7	1.6	—	—	—	+
54	51	4.1	2.5	1.3	58	4.1	2.7	1.3	—	—	—	+
54	59	3.9	2.5	1.2	68	3.9	2.7	1.3	—	—	—	+
Average—									Total—			
45.1	38.6	3.25	2.18	1.20	38.1	3.23	2.22	1.22	2	3	0	25

TABLE 8.—*Measurements of the Lacuna Vasorum and Associated Structures in Thirty Men*

Age, Years	Length, Cm.	Estimated Weight, Pounds	Right Side: Lacuna Vasorum, Sq. Mm.	Right Side: Poupart's Ligament, Cm.	Right Side: Vein: Caliber, Mm.	Right Side: Vein: Wall, Mm.	Right Side: Artery: Caliber, Mm.	Right Side: Artery: Wall, Mm.	Left Side: Lacuna Vasorum, Sq. Mm.	Left Side: Poupart's Ligament, Cm.	Left Side: Vein: Caliber, Mm.	Left Side: Vein: Wall, Mm.	Left Side: Artery: Caliber, Mm.	Left Side: Artery: Wall, Mm.	Hernial Sacs: Inguinal	Hernial Sacs: Femoral
19	166	120	300	13.6	10.8	0.5	5.4	0.9	240	13.6	10.8	0.6	8.2	1.0	—	—
37	169	110	390	12.3	9.8	0.4	6.1	1.0	270	12.2	9.4	0.4	5.8	1.1	—	—
39	177	170	310	14.6	12.0	0.5	5.8	1.3	280	14.6	12.4	0.3	3.8	1.2	—	—
39	175	170	320	12.7	9.2	0.6	5.3	1.1	300	12.8	9.4	0.6	5.1	1.0	—	—
44	172	160	430	13.1	9.6	0.7	4.8	1.4	420	13.1	10.1	0.6	4.9	1.5	—	—
45	173	120	640	12.4	8.5	0.7	4.2	1.3	550	12.2	8.4	1.0	4.1	1.2	—	—
45	181	135	510	13.9	8.9	0.6	5.6	1.1	490	13.9	8.7	0.5	5.7	1.0	—	—
53	168	140	390	13.4	9.8	1.0	7.0	1.2	430	13.4	9.6	1.0	7.2	1.2	—	—
54	177	159	390	11.5	12.6	0.5	5.4	1.0	350	11.4	11.2	0.4	5.4	1.5	—	Right
55	176	160	360	11.3	9.1	0.6	7.8	1.1	310	11.1	9.2	0.6	8.4	1.2	—	—
57	165	120	420	12.6	11.2	0.5	6.8	1.2	430	12.2	10.8	0.5	7.0	1.1	—	—
59	189	140	490	17.0	10.1	0.6	8.4	1.0	400	17.1	9.4	0.6	8.3	1.2	—	—
59	174	180	590	12.8	14.2	0.6	9.6	1.1	580	12.9	12.0	0.6	9.4	1.2	—	—
59	165	140	320	11.9	11.8	0.7	7.0	1.6	280	11.8	12.0	0.7	7.2	1.5	—	—
59	168	140	420	12.3	9.6	0.7	8.2	1.2	460	12.3	9.4	0.6	7.0	1.3	—	Right
60	173	160	530	13.3	10.2	0.8	7.0	1.3	510	13.3	9.8	0.8	6.3	1.4	—	Right
60	177	160	590	12.8	9.0	0.5	5.2	1.2	550	12.5	9.2	0.5	5.4	1.2	—	—
61	161	160	520	12.3	12.0	0.6	5.2	1.2	340	12.6	10.4	0.6	5.4	1.4	Left	—
62	175	160	660	14.5	11.8	1.7	7.2	1.1	780	14.3	11.2	0.7	7.7	1.3	Right	—
62	170	160	420	11.3	8.2	0.6	6.4	1.6	350	11.3	7.8	0.6	5.7	1.7	—	—
65	171	180	360	12.6	12.0	0.6	8.9	0.9	400	12.5	11.2	0.5	9.4	1.1	Right	—
68	174	160	250	11.6	12.0	0.6	8.3	1.3	300	12.0	16.0	0.7	8.7	1.3	—	—
69	170	165	640	14.4	11.8	0.7	7.7	1.1	700	13.9	11.0	0.6	7.6	1.0	Bilateral	—
69	175	160	540	12.3	8.0	0.8	6.4	1.6	500	12.2	8.3	0.7	5.2	1.2	—	—
69	167	170	370	12.8	11.2	0.6	5.2	1.3	340	12.6	10.4	0.6	5.4	1.4	Left	—
70	178	190	400	13.0	10.0	0.5	8.0	1.1	410	13.1	10.2	0.5	7.4	1.0	—	—
71	175	200	450	15.4	10.0	0.6	8.0	1.8	380	15.4	9.4	0.6	8.4	1.8	Bilateral	—
71	186	150	500	12.4	9.8	0.7	5.7	1.3	390	12.4	9.0	0.8	7.7	1.4	—	—
77	167	150	640	13.1	10.2	0.6	9.7	1.0	650	13.1	10.2	0.7	8.6	1.1	—	—
79	173	145	400	13.7	9.6	0.7	7.0	1.4	410	13.8	9.8	0.7	7.5	1.3	—	—
Average—															Total—	
58	173		451	13.03	10.43	0.68	6.77	1.22	430.6	12.97	10.25	0.63	6.8	1.26	8	3

TABLE 9.—*Measurements of the Lacuna Vasorum and Associated Structures in Thirty Women*

Age, Years	Length, Cm.	Estimated Weight, Pounds	Right Side: Lacuna Vasorum, Sq. Mm.	Right Side: Poupart's Ligament, Cm.	Right Side: Vein: Caliber, Mm.	Right Side: Vein: Wall, Mm.	Right Side: Artery: Caliber, Mm.	Right Side: Artery: Wall, Mm.	Left Side: Lacuna Vasorum, Sq. Mm.	Left Side: Poupart's Ligament, Cm.	Left Side: Vein: Caliber, Mm.	Left Side: Vein: Wall, Mm.	Left Side: Artery: Caliber, Mm.	Left Side: Artery: Wall, Mm.	Hernial Sacs: No. Children	Hernial Sacs: Inguinal	Hernial Sacs: Femoral
18	150	110	280	10.9	9.0	0.4	5.8	1.1	350	10.9	9.2	0.4	5.2	1.1	0	—	—
21	163	130	260	12.2	8.0	0.4	6.8	1.0	250	12.0	9.0	0.4	7.0	1.0	0	—	—
22	155	125	280	11.4	8.0	0.6	3.7	1.0	320	11.5	7.4	0.6	3.4	1.0	1	—	—
27	165	135	230	11.2	9.8	0.5	4.7	0.8	270	11.2	11.2	0.5	5.0	0.9	0	—	—
28	159	110	230	12.4	9.0	0.3	5.0	1.0	260	12.2	9.4	0.4	4.8	0.9	1	—	—
28	168	120	260	13.3	10.4	0.4	6.2	1.0	290	13.3	10.2	0.4	5.8	1.0	5	—	—
35	159	135	300	12.3	11.0	0.9	5.6	1.4	380	12.3	10.8	0.8	5.8	1.4	0	—	—
38	166	110	470	11.8	9.2	0.6	4.8	1.0	350	11.6	8.3	0.5	4.4	1.2	0	—	Right
39	154	110	280	13.4	8.4	0.5	4.8	0.9	290	13.6	8.0	0.4	5.2	0.9	0	—	—
39	158	100	320	12.8	11.0	0.4	5.8	1.0	300	12.8	9.8	0.4	5.3	0.9	9	—	Right
40	155	130	280	12.9	8.4	0.7	5.4	1.2	250	13.1	8.2	0.6	5.1	1.1	7	—	—
41	152	100	420	13.1	6.2	0.5	3.1	1.0	370	13.1	6.6	0.5	3.1	1.0	1	—	—
42	158	150	300	11.6	10.2	0.5	4.8	0.9	340	11.7	9.8	0.6	5.0	0.9	6	—	—
44	157	110	280	13.2	11.4	0.6	5.4	1.0	360	13.2	11.4	0.7	5.8	1.2	0	—	—
44	167	120	320	12.8	5.4	0.6	4.6	1.0	370	12.7	5.6	0.6	4.4	1.0	4	—	—
45	162	140	370	14.0	7.8	0.7	3.8	1.2	400	13.9	8.2	0.7	4.1	1.2	3	—	—
48	164	145	410	12.8	9.6	0.6	5.6	1.2	480	12.8	9.0	0.7	6.0	1.3	3	—	—
55	162	110	380	13.1	12.0	0.5	6.3	1.1	400	13.0	16.0	0.5	6.2	1.2	8	—	—
55	154	175	300	11.4	10.4	0.5	6.8	1.1	300	11.4	9.6	0.4	6.4	1.0	1	—	—
55	167	130	410	14.3	9.3	0.6	7.5	1.2	490	14.4	9.5	0.7	7.2	1.2	7	Left	—
56	160	110	330	12.0	7.0	0.7	5.4	1.3	330	12.3	7.2	0.7	5.8	1.4	2	—	—
56	158	110	230	12.8	9.8	0.7	7.6	1.0	220	13.0	9.5	0.7	7.2	1.0	0	—	—
61	160	136	530	12.2	8.3	0.8	5.2	1.2	480	12.1	8.0	0.7	4.8	1.3	8	Right	—
62	165	180	330	12.7	11.4	0.6	9.2	1.2	430	12.8	11.0	0.6	9.3	1.1	11	—	—
62	168	180	510	12.8	10.0	0.5	4.2	1.2	350	12.9	9.2	0.5	4.8	1.3	9	—	—
63	153	150	270	12.6	6.6	0.6	5.3	1.2	220	12.5	7.0	0.5	5.5	1.0	6	—	—
66	158	145	400	11.4	10.4	0.6	6.0	0.9	330	11.6	10.4	0.7	5.8	1.0	12	—	Bilat.
68	163	150	320	12.7	8.8	0.7	5.0	1.2	300	12.5	9.3	0.8	6.2	1.4	5	—	—
73	155	160	1100	11.6	9.4	1.3	7.4	1.9	1050	11.2	9.1	0.9	7.4	1.8	3	Left	Right
78	153	160	420	12.7	9.6	0.4	7.3	1.5	380	12.9	9.8	0.4	7.4	1.5	2	—	—
Average—															Total—		
47	160		360.6	12.5	9.19	0.58	5.04	1.12	363.7	12.5	9.26	0.58	5.65	1.14	3	5	

TABLE 10.—*Measurements of the Lacuna Vasorum and Associated Structures in Eight Infants and Children—Both Sexes*

				Right Side						Left Side						Hernial Sacs	
						Vein		Artery				Vein		Artery			
Age	Sex	Length, Cm.	Estimated Weight, Pounds	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.	Lacuna Vasorum, Sq. Mm.	Poupart's Ligament, Cm.	Caliber, Mm.	Wall, Mm.	Caliber, Mm.	Wall, Mm.	Inguinal	Femoral
8 mo.	M	69	22	86	5.7	3.6	...	2.3	...	97	5.7	2.9	...	2.0	...	—	—
8 yr.	M	120	60	210	8.6	5.3	0.3	2.8	0.5	150	8.4	4.8	0.3	2.9	0.5	—	—
14 yr.	M	135	90	230	10.1	5.8	0.4	3.7	1.0	190	9.9	6.0	0.5	4.0	1.0	—	—
6 mo.	F	58	10	65	5.1	2.4	...	1.7	...	71	5.0	2.6	...	2.0	...	—	—
8 mo.	F	61	12	80	4.6	...	...	...	...	83	4.5	...	...	...	...	—	—
14 yr.	F	155	100	290	11.4	8.2	0.5	4.4	0.8	240	11.4	8.4	0.5	4.1	0.8	—	—
14 yr.	F	169	100	220	12.9	13.0	0.9	4.4	1.0	190	13.0	13.5	0.6	4.0	1.0	—	—
16 yr.	F	160	95	280	13.5	7.8	0.4	4.2	0.8	260	13.5	7.0	0.4	4.2	0.8	—	—

The procedure used in nearly every group can be divided into two classes: the numerical and graphical analytic methods. In the former were included the calculation of the numerical average of each set of figures, the determination of the coefficient of variability for each group of figures and the calculation of the Pearsonian coefficient of correlation.[2]

2. Pearson's formula for the coefficient of correlation is:

$$r = \frac{\Sigma\ (XY)}{N\ \acute{o}_1\ \acute{o}_2}$$

where $\Sigma\ (XY)$ equals the sum of the X deviations multipled by the Y deviations, N is the number of cases, $\acute{o}_1$ is the standard deviation of X, and $\acute{o}_2$ is the standard deviation of Y.

The standard deviation is obtained by the following formula:

$$\sqrt{\frac{\Sigma d^2}{N}}$$

with d^2 representing the sum of the deviations squared.

The probable error of the coefficient of correlation is obtained by the formula:

$$\text{P.E.} = \frac{0.67\ (1 - r^2)}{\sqrt{N}}$$

where r represents the coefficient of correlation and N the number of cases.

The following conventions are often applied to the interpretation of the coefficient of correlation (King, W. I.: The Elements of Statistical Method, New York, The Macmillan Company, 1916, p. 215):

1. If r is less than the probable error, there is no evidence whatever of correlation.

2. If r is more than six times the size of the probable error, the existence of correlation is a practical certainty.

3. If r is less than 0.30, the correlation cannot be considered at all marked.

4. If r is above 0.50, there is decided correlation.

SUMMARY OF OBSERVATIONS

Premature and New-Born Infants.—The average length for both sexes in the 34 male premature and new-born infants and the 30 females was very nearly equal—45.3 cm. for the males and 45.1 cm. for the females. In most cases the measurements of the male were quite appreciably larger than the female. The right side in nearly all cases was also slightly larger than the left, except in the case of the vessels.

The average area of the lacuna vasorum at birth (an average of all infants between the crown-heel length of 48 and 54 cm.) was 47 sq. mm. for the females and 49 sq. mm. for the males.

Among the 34 males the processus vaginalis was closed in 9, open bilaterally in 18, open on the right in 6 and on the left in 1. Among the 30 females it was closed in 25, open bilaterally in 2, open on the right side in 3 and on the left side in none.

Adults.—In adults the average length for the males was 172.9 cm. and for the females 159.6 cm. The difference in the size of the measurements corresponds fairly well with this inequality. The average age for the males was also higher—57.8 years and 46.9, respectively. The lacuna vasorum was found to be absolutely and also relatively larger in the male than in the female. In females the average crown-heel length was 159.6 cm. and the average lacunar area was 360 sq. mm. Then, with an average crown-heel length of 173 cm. for the males, the lacunar area of the latter should measure about 390 plus sq. mm., while it did measure 440 sq. mm., showing a definite increase over the female of about 50 sq. mm. The average measurements on the right side in most instances was greater than on the left, except in the case of the vessels.

In the 60 adults there were 6 femoral hernial sacs present, 3 in each of the sexes. In 5 the sacs were small, on the average from about ¼ to 1 inch (1.9 to 2.5 cm.) in depth. In the sixth, which was present

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The coefficient of variability was obtained by the following formula:

$$\frac{\acute{o}}{M} \times 100$$

where $\acute{o}$ is the standard deviation and M the arithmetic average. It is read in per cent.

The second type consists of field graphs in which the central tendency was established by means of a regression line. The points for the latter were obtained by the use of the following formula:

$$Y = r\frac{\acute{o}\,Y}{\acute{o}\,X}X - r\frac{\acute{o}\,Y}{\acute{o}\,X}\overline{X} + \overline{Y}$$

where Y is the ordinate, r the coefficient of correlation, $\acute{o}\,Y$ the standard deviation of Y, $\acute{o}\,X$ the standard deviation of X, X the abscissa, $\overline{X}$ the mean of the abscissa and $\overline{Y}$ the mean of the ordinate.

in a female specimen, the sac was large and overlaid Poupart's ligament. In this specimen there were found the largest lacunae vasorum of the entire series, 1,100 sq. mm. on the right (the side of the hernia) and 1,050 sq. mm. on the left. However, on the left side there was no evidence of hernia. Associated with this large right femoral hernia was an indirect left inguinal hernia. Five of the 6 sacs were on the right side. All sacs were empty.

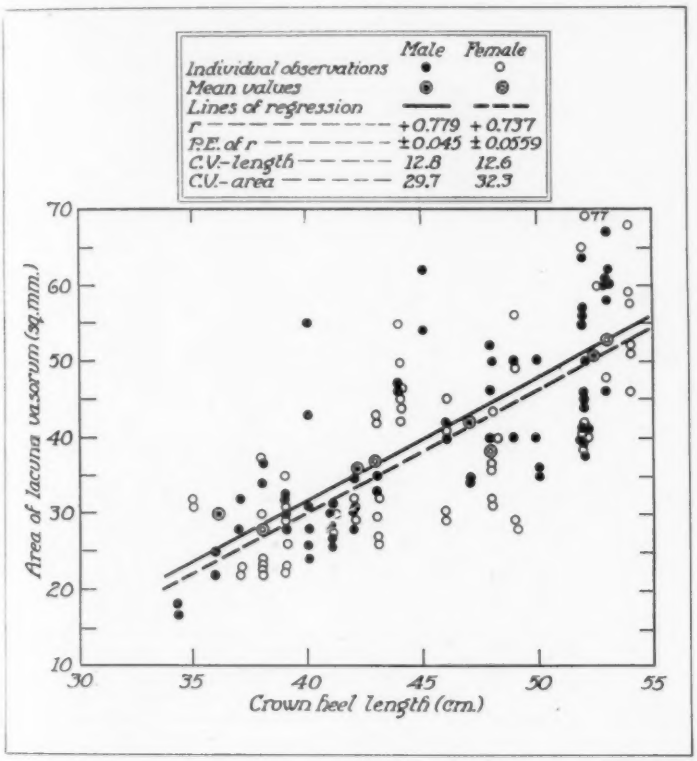

Fig. 4.—Field graph showing the area of the lacuna vasorum in premature and new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

There were also 7 cases with indirect inguinal hernial sacs; the one already described as associated with a femoral, 1 bilateral, 4 left-sided and 2 right-sided. None of these was very large. In 1 case bilateral obturator hernial sacs were also observed. No special search, however, was made for these in all cases examined. As far as is known, in no case was the subject aware that a hernia was present.

Of the 30 women examined, 8 gave a history of no pregnancies, 4 of only 1 pregnancy and 18 of 1 or more. In the latter group the

average number of children for each was 6 plus. The area of the lacuna vasorum in the group of 8 without children was 290 sq. mm., in the group with only 1 child it was 310 sq. mm., and in the group with more than 1 it was highest, 370 sq. mm. One of the group of 8 nulliparous women had one of the femoral peritoneal diverticula.

Area of the Lacuna Vasorum According to Crown-Heel Length in Premature and New-Born Infants.—The coefficient of correlation for

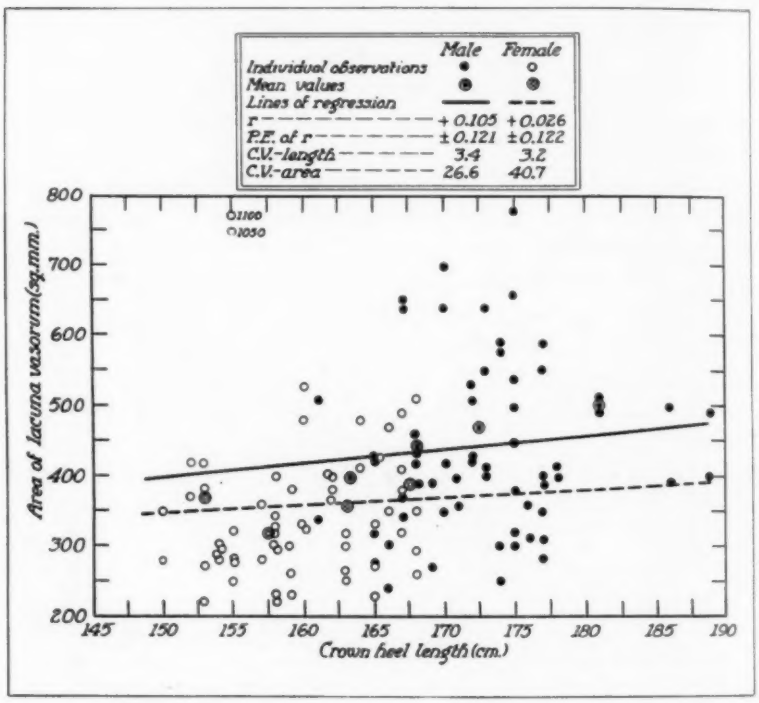

Fig. 5.—Field graph showing the area of the lacuna vasorum in adults according to crown-heel length; the central tendency is indicated by regression lines.

the males in this group was + 0.779 with a probable error of ± 0.045, and for the females it was + 0.737 with a probable error of ± 0.0559. This high correlation was demonstrated in figure 4.

Area of the Lacuna Vasorum According to Crown-Heel Length in Adults.—No correlation of significance could be demonstrated graphically or numerically in this group. The coefficient of correlation for the males was + 0.105 with a probable error of ± 0.121, and for the females it was — 0.026 with a probable error of ± 0.122 (fig. 5).

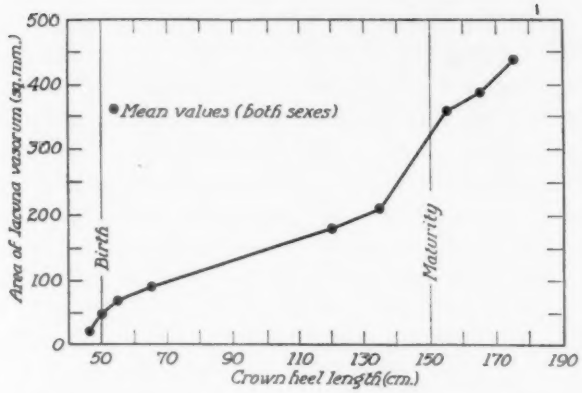

Fig. 6.—The area of the lacuna vasorum in premature and new-born infants, children and adults according to crown-heel length; the average of both sides and both sexes is shown.

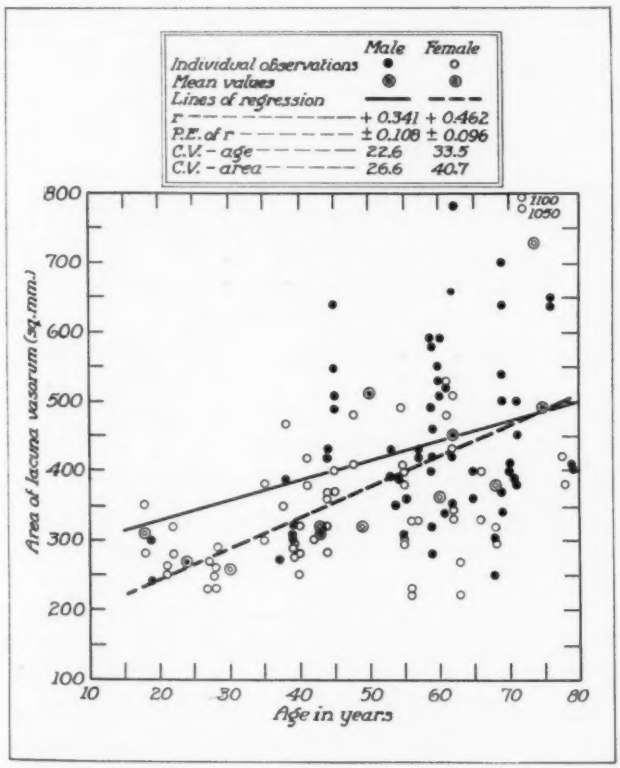

Fig. 7.—Field graph showing the area of the lacuna vasorum in adults according to age; the central tendency is indicated by regression lines.

In figure 6 it is apparent that when an average of all of the cases was taken for each of three long intervals (10 cm. crown-heel length) there was a definite increase in the area of the lacuna vasorum according to length; but it must also be remembered that this increase in size is probably accounted for by the fact that the larger persons are all males, and that the males have larger lacunae in proportion to length than do females.

Area of the Lacuna Vasorum According to Age in Adults.—A fair degree of correlation exists between the area of the lacuna vasorum and age, especially in the female group. The coefficient of correlation for the males was + 0.341 with a probable error of ± 0.108, and for

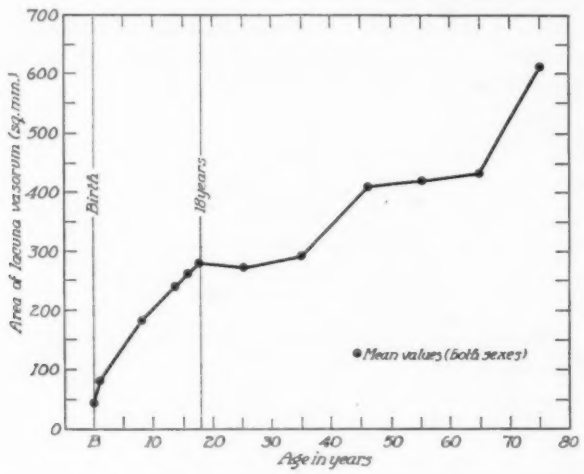

Fig. 8.—Area of the lacuna vasorum from birth to old age.

the females + 0.462 with a probable error of ± 0.096. This correlation was further demonstrated in figure 6.

In figure 7 is shown the growth in size of the lacuna vasorum from birth to old age. Between the ages of 18 and 35, there is a flat area which may be of significance, although this again occurs between the ages of 45 and 65.

Length of Poupart's Ligament According to Crown-Heel Length in Premature and New-Born Infants.—There is good correlation between Poupart's ligament and length in this group. For the males the coefficient of correlation is + 0.846 with a probable error of ± 0.032, and for the females it is + 0.825 with a probable error of ± 0.039. Figure 9 shows this still further.

Area of the Lacuna Vasorum According to Length of Poupart's Ligament in Premature and New-Born Infants.—Again the correlation

is good. For the males it is + 0.681 with a probable error of ± 0.0615, and for the females + 0.70 with a probable error of ± 0.062. These facts are demonstrated in graphical form in figure 10.

Length of Poupart's Ligament According to Crown-Heel Length in Adults.—There is definite but not a great deal of correlation in this group. For the males the coefficient is +0.479 with a probable error of ±0.094, while for the females it is + 0.364 with a probable error

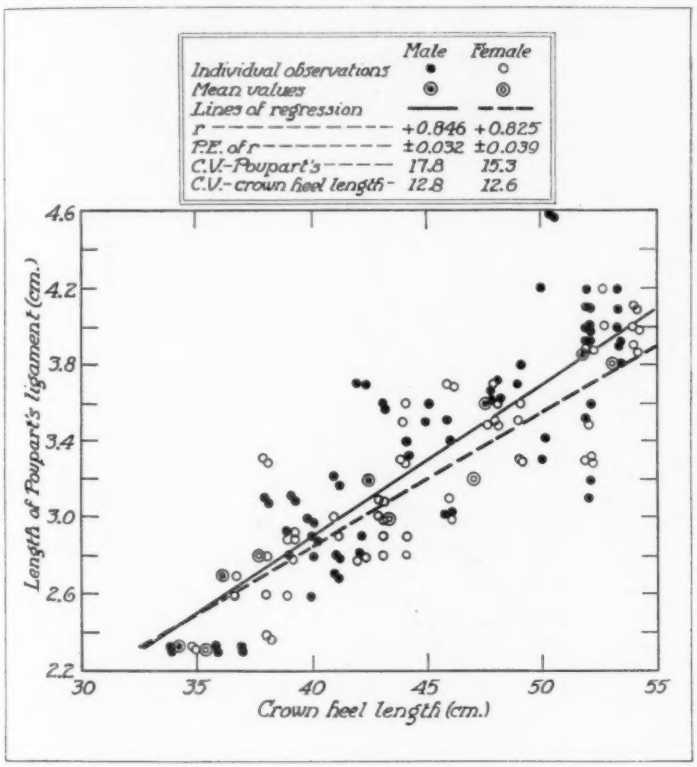

Fig. 9.—Field graph showing the length of Poupart's ligament in premature and new-born infants according to crown-heel length; the central tendency is indicated by regression lines.

of ± 0.105. Figure 11 demonstrates still further the degree of correlation in each case.

Area of Lacuna Vasorum According to Length of Poupart's Ligament in Adults.—There was possibly a small amount of correlation in this group, the males showing a coefficient of correlation of + 0.295 with a probable error of ± 0.111. The females showed none at all;

in fact, the coefficient was —0.101 with a probable error of ± 0.121. Figure 12 illustrates this lack of any definite correlation.

Caliber of the Femoral Artery and Vein According to Crown-Heel Length in Premature and New-Born Infants.—The correlation was good in both the artery and the vein. The coefficient of correlation between the caliber of the veins and crown-heel length for the males was + 0.483 with a probable error of ± 0.089, while for the females

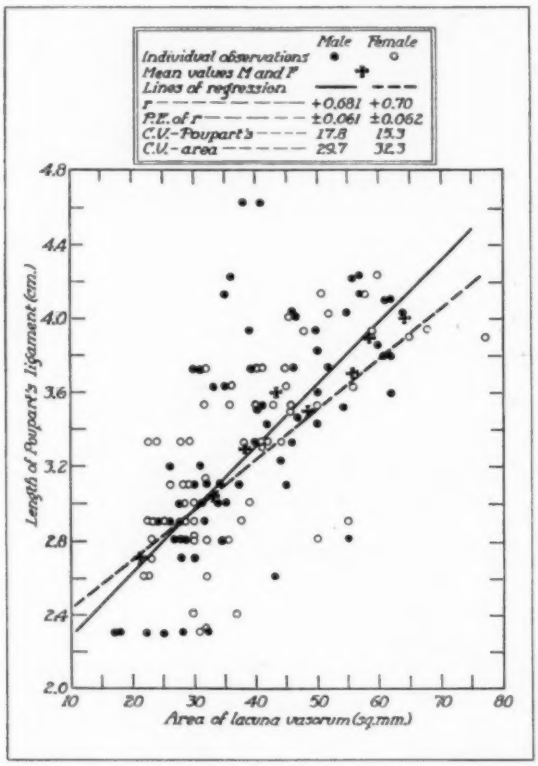

Fig. 10.—Field graph showing the area of lacuna vasorum in premature and new-born infants according to the length of Poupart's ligament; the central tendency is indicated by regression lines.

the coefficient was + 0.463 with a probable error of ± 0.097. For the arteries, the coefficient was + 0.547 with a probable error of ±0.0818 for the males, and for the females it was + 0.565 with a probable error of ± 0.0847. This is further demonstrated in figure 13, which shows it graphically for the veins, and in figure 14 for the arteries.

Caliber of the Femoral Vein According to the Area of the Lacuna Vasorum in Premature and New-Born Infants.—There was fairly good

correlation in the males for these measurements, with a coefficient of $+0.537$ and probable error of ± 0.083; but in the females the correlation was found to be barely present, the coefficient being $+0.257$ with a probable error of ± 0.116. Graphically, the correlation is definitely present and is illustrated in figure 15.

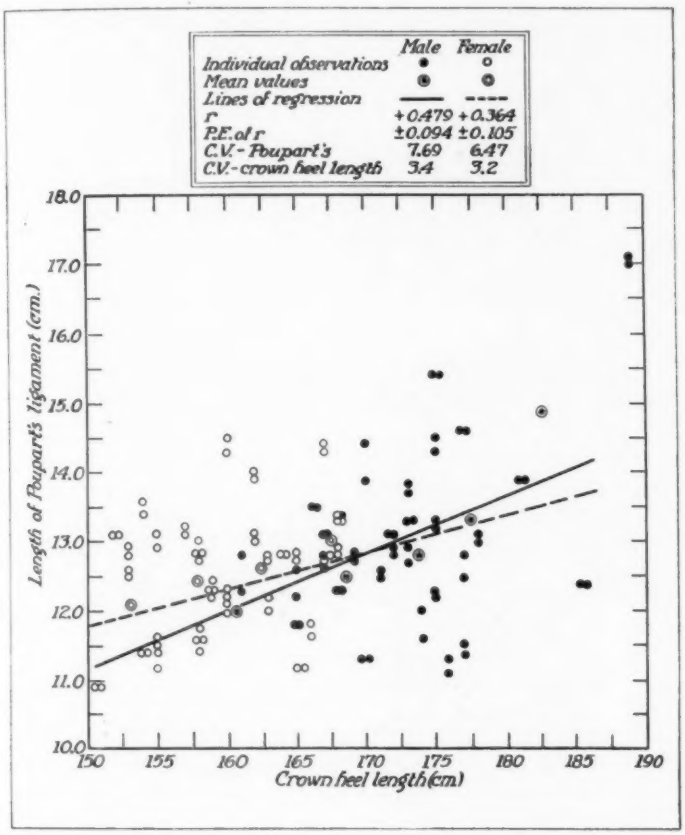

Fig. 11.—Field graph showing the length of Poupart's ligament in adults according to the crown-heel length; the central tendency is indicated by regression lines.

Size of the Femoral Vein and Artery According to Age in Adults.—There was no evidence of correlation between veins and age in adults. The coefficient for the males was $+0.059$ with a probable error of ± 0.122, and for the females $+0.087$ with a probable error of ± 0.121. In the arteries, however, there was fairly good correlation. The coefficient for the males was $+0.447$ with a probable error of ± 0.098, and for the females it was $+0.421$ with a probable error of ± 0.082. Figure

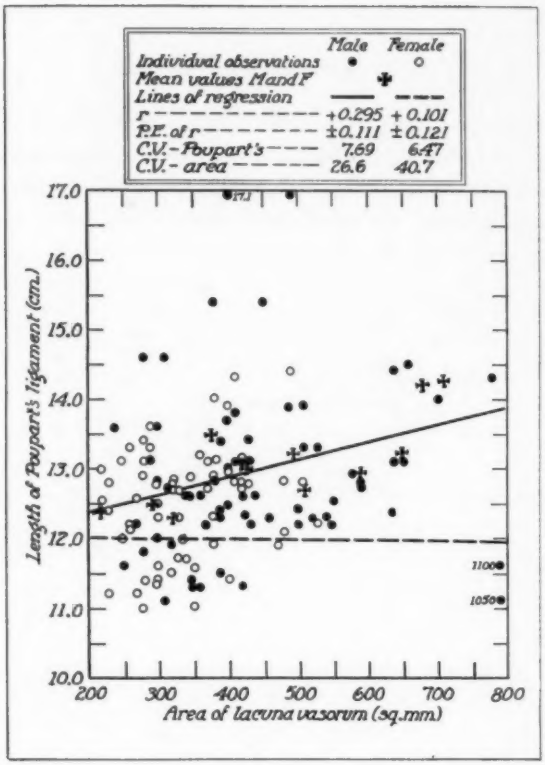

Fig. 12.—Field graph showing the area of the lacuna vasorum in adults according to the length of Poupart's ligament; the central tendency is indicated by regression lines.

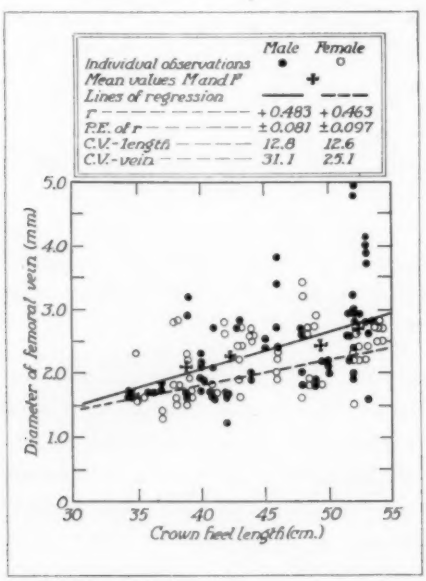

Fig. 13.—Field graph showing the caliber of the femoral vein in premature and new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

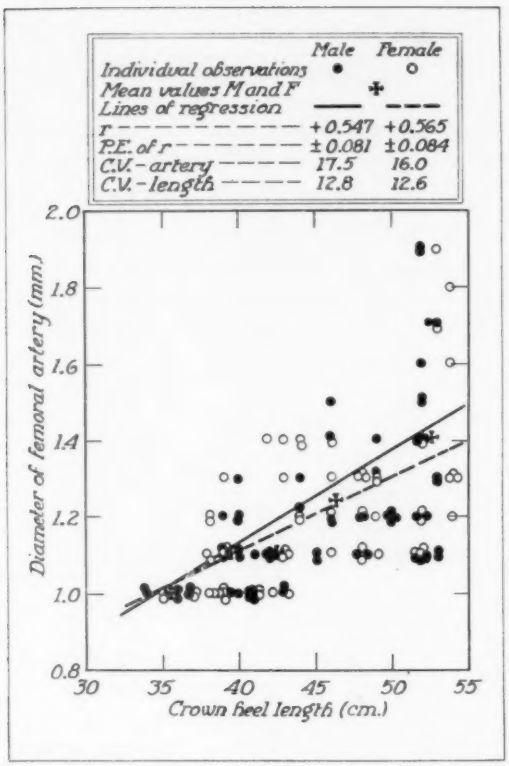

Fig. 14.—Field graph showing the caliber of the femoral artery in premature and in new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

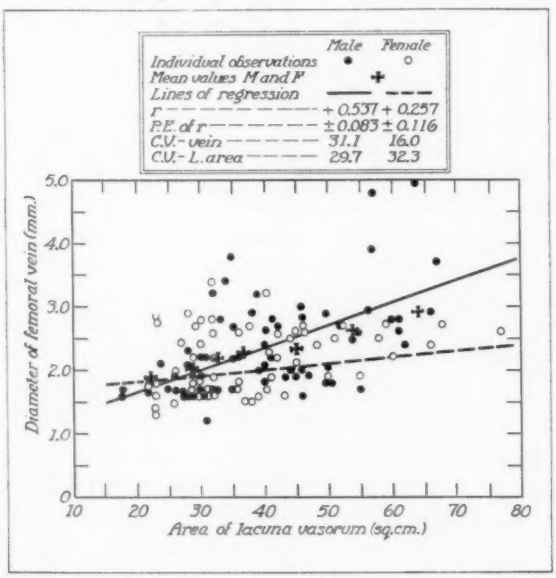

Fig. 15.—Field graph showing the area of the lacuna vasorum in premature and new-born infants according to the caliber of the femoral vein; the central tendency is indicated by regression lines.

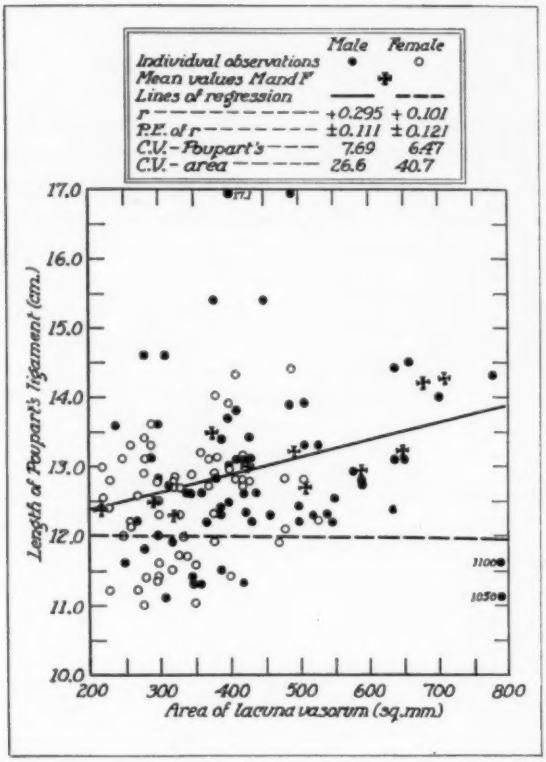

Fig. 12.—Field graph showing the area of the lacuna vasorum in adults according to the length of Poupart's ligament; the central tendency is indicated by regression lines.

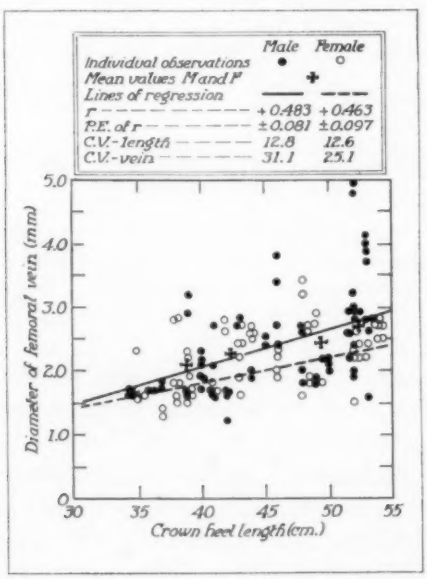

Fig. 13.—Field graph showing the caliber of the femoral vein in premature and new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

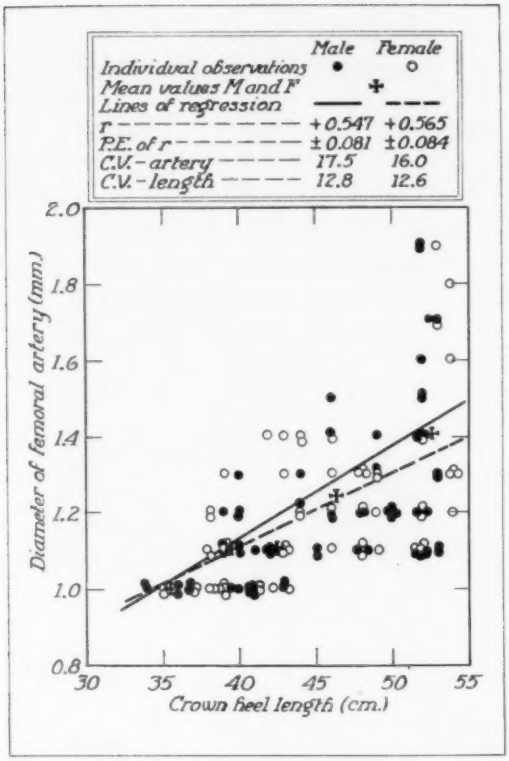

Fig. 14.—Field graph showing the caliber of the femoral artery in premature and in new-born infants according to the crown-heel length; the central tendency is indicated by regression lines.

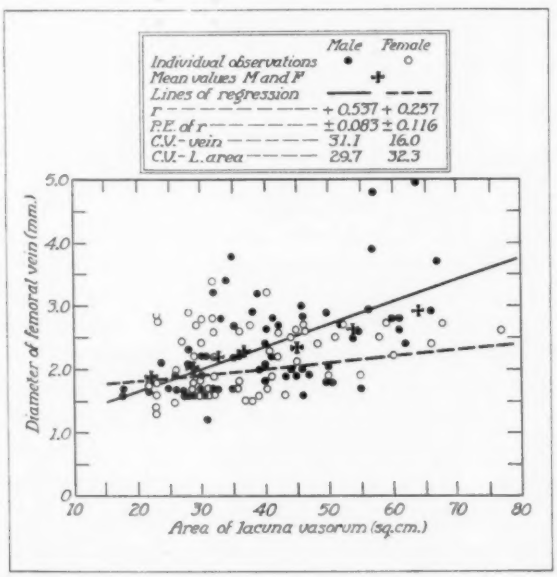

Fig. 15.—Field graph showing the area of the lacuna vasorum in premature and new-born infants according to the caliber of the femoral vein; the central tendency is indicated by regression lines.

16 illustrates these facts for the veins, while figure 17 does the same for the arteries.

Size of Femoral Arteries According to Area of Lacuna Vasorum in Adults.—There was no correlation found between the area of the lacuna vasorum and the femoral vein. The coefficient of correlation for the entire group was + 0.088 with a probable error of ± 0.0606. In the

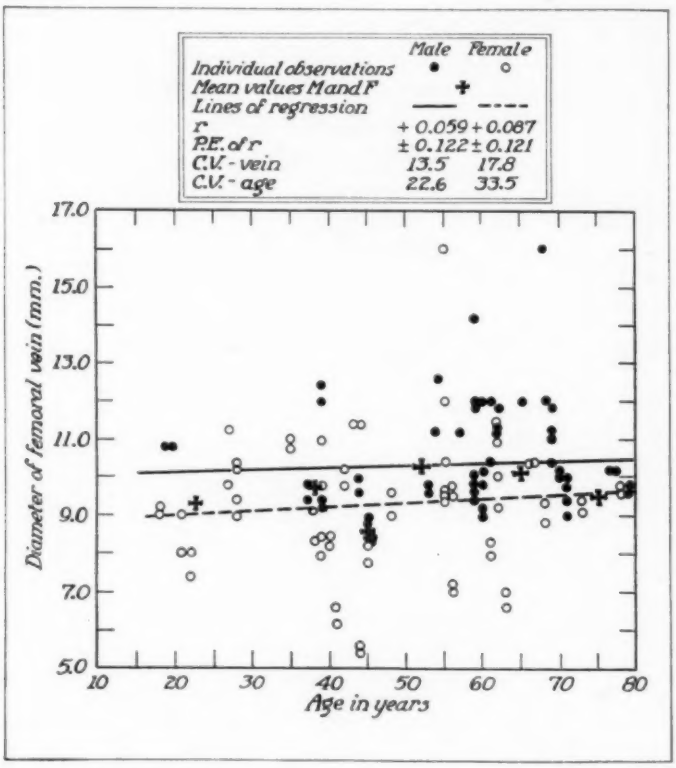

Fig. 16.—Field graph showing the caliber of the femoral vein in adults according to age; the central tendency is indicated by regression lines.

arteries there was some correlation present, with a coefficient of + 0.250 and probable error of ± 0.056.

Caliber of the Femoral Vessels According to Crown-Heel Length in Adults.—No correlation was found in this group. The coefficient of correlation for males as to size of veins and crown-heel length was — 0.197 with a probable error of ± 0.117, and for females it was + 0.174 with a probable error of ± 0.118. In the arteries it was about the same, with a coefficient of correlation for the males of + 0.041 and probable error of ± 0.122, and for the females + 0.096 with a

probable error of ± 0.121. No graphs were made as it was evident that no correlation existed between the two.

Thickness of the Walls of the Femoral Vessels According to Age in Adults.—There was possibly some correlation present for the venous walls and good correlation for the arterial walls. For the males the coefficient of correlation for the arterial walls according to age was + 0.330 with a probable error of ± 0.109, while for the females it

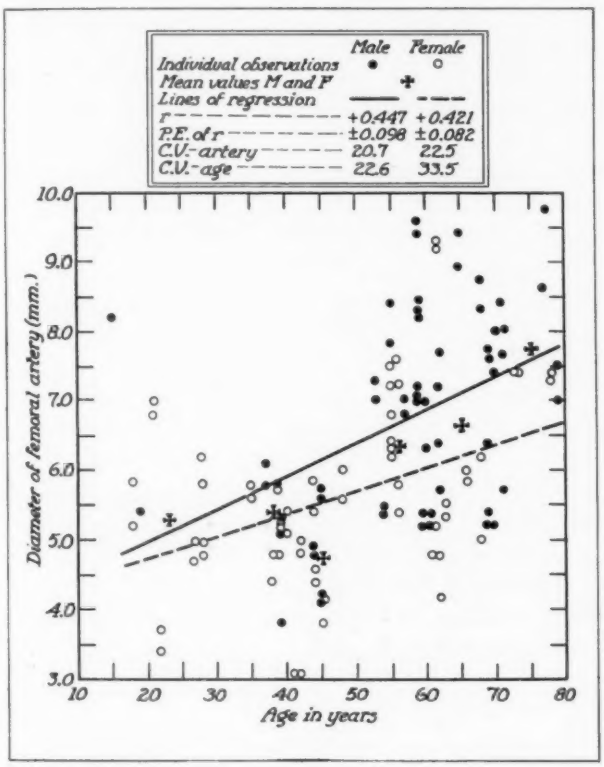

Fig. 17.—Field graph showing the caliber of the femoral artery in adults according to age; the central tendency is indicated by regression lines.

was + 0.560 with a probable error of ± 0.084. In the venous walls the coefficient was + 0.232 with a probable error of ± 0.115 for the males, and + 0.443 with a probable error of ± 0.093 for the females. Figure 18 demonstrates the foregoing figures for the arteries. No graphic representation was made for the veins.

Potential Space Available for the Development of Femoral Hernia.—When the sum of the cross-section areas of the two femoral vessels are subtracted from the area of the lacuna vasorum, the available space

left is larger for males than for females. For males, this was 451 sq. mm. minus 173.9 sq. mm., or 277.1 sq. mm.; and for females, it amounted to 362.1 sq. mm. minus 133.6 sq. mm., or 228.5 sq. mm., a difference of about 50 sq. mm.

COMMENT ON CLINICAL AND ANATOMIC FINDINGS

From this and other clinical studies the following outstanding facts present themselves. Femoral hernias are relatively uncommon before

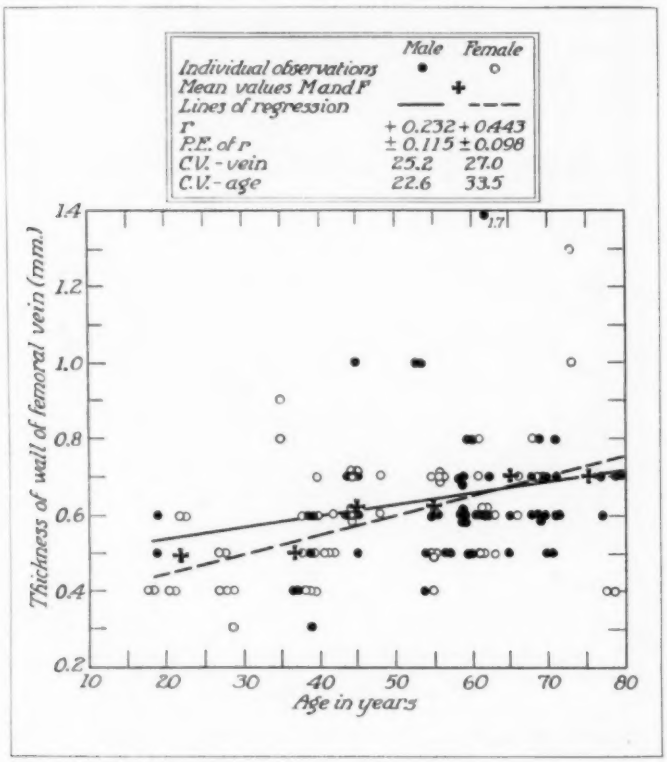

Fig. 18.—Field graph showing the thickness of the walls of the femoral vein in adults according to age; the central tendency is indicated by regression lines.

the age of 20 and probably have never been seen before the age of 2. They increase in frequency with age. Females afflicted outnumber males, and mothers, the childless. Heavy manual labor, the presence of asthma, chronic cough or debilitating diseases often are factors present in the appearance, if not in the original formation, of this type of hernia. Femoral hernia is eight times more liable to become

strangulated than inguinal hernia. A large number of the sacs seen at operation are empty. Most of them are small even when they contain omentum or bowel. When abdominal contents are present, they are frequently strangulated. Normal bowel was not present in any of the four hernial sacs in our series; all were strangulated. Most sacs are surrounded by a definite layer of fat. Recurrences following hernial repair, including removal of the sac, are common.

Anatomic findings demonstrate the following facts: Many peritoneal diverticula are found in adult bodies examined after death, which were unrecognized by the patient or physician during life. As a rule, all are found to be empty. There are as many of these pouches in males as in females. No femoral diverticula were ever found in otherwise normal new-born infants.

Women who have borne children are seen more often with femoral hernia clinically, probably because of the added strain occurring during labor which forces omentum or bowel into the sac, which has already been formed, and thereby brings its presence to the attention of the patient. In dead bodies studied, the incidence of femoral hernia sacs is the same in both sexes. The fact that the lacuna vasorum increases its area with age doubtless is a factor in the increased frequency of these hernia in the later decades of life. This increase is undoubtedly due to the relaxation of the ligaments, fascia and muscles, which occurs at this time.

Poupart's ligament is shorter in the female than in the male. The foramen vasorum is smaller in the female than in the male, even when considered proportionately according to size. The caliber of the femoral vessels is also smaller in women than in men. The size of the femoral ring (or, to be more exact, the area of the space available for the development of a femoral hernia) calculated by subtracting the diameter of the cross-section area of the two vessels from the total area of the lacuna vasorum is also smaller in females.

The lacuna vasorum increases in size with age as do the femoral arteries. This starts in early fetal life and continues to old age. The femoral vein shows similar correlation until adult life is reached; thereafter, the caliber varies with changes in weight and height.

Because femoral hernial sacs are frequently found in adult bodies, especially in the later years of life, and never in new-born infants, the conclusion must be that these diverticula are acquired. They are usually empty, but when abdominal organs once enter the sac they frequently become strangulated. It seems highly improbable that an organ that cannot be easily reduced back into the abdominal cavity could originally have much influenced the formation of that sac.

Traction on the peritoneum drawing it down through the lacuna vasorum is the most logical reason for the formation of all femoral hernial sacs, but what produces this traction is extremely difficult to explain. Abnormal gubernacular bands have been considered by some to be the cause, but even if the gubernaculum could influence the descent of the peritoneum it would do this extremely early in life and not after birth. The other possibility lies in the covering of fat that is present normally in the crural region and is practically always found covering the fundus of the sacs. How fat can do this no one has as yet explained, but a similar situation is probably present in the formation of the hernia through the vascular foramina of the linea alba, and it seems reasonable that it can occur in the femoral region as well.

CONCLUSIONS

1. Femoral hernial sacs are never congenital. They are always acquired and are produced by traction and not by pressure.

2. Males have as many femoral peritoneal diverticula as females, but clinically femoral hernia are found twice as often in women as in men.

3. The lacuna vasorum increases in size in both sexes from fetal life to old age. This enlargement of the lacuna vasorum favors the production of femoral hernia because it allows the force of traction to act to better advantage.

4. The lacuna vasorum is smaller in the female than in the male.

5. Poupart's ligament is shorter in females than males.

6. There is very little, if any, correlation between the size of the lacuna vasorum and the length of Poupart's ligament in adults. In fetal life and early infancy there is a high correlation.

7. The femoral artery increases in caliber from fetal life to old age.

8. The femoral vein increases in caliber up to adult life and then varies according to other factors such as height and weight.

9. The walls of the femoral artery and vein increase in thickness with age.

10. There is no correlation between the size of the lacuna vasorum and the size of the vessels in adults; during fetal life and early infancy this correlation is good.

11. Extirpation of the hernial sac with adequate closure of the femoral orifice offers the patient the best hope of permanent cure.

12. The available space for the development of a femoral hernia is smaller in the female than in the male; that is, the difference between the sum of the areas of the two femoral vessels subtracted from the total area of the lacuna vasorum, is greater in males than it is in females.

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CHANGES IN THE WALL OF THE BLADDER SECONDARY TO PROSTATIC OBSTRUCTION

THEIR SIGNIFICANCE IN PROSTATIC SURGERY

D. K. ROSE, M.D.
ST. LOUIS

A consideration of prostatic obstruction and the treatment for it entails: first, an analysis of the variation from normal function of the posterior urethra, internal sphincter, trigon and wall of the bladder; second, a consideration of how the type and location (relative to the internal sphincter) of the obstructing mass may bring about such variation and so specifically alter the action of these parts as to account for the marked dissimilarity in individual cases with regard to symptoms, infection, both local and generalized, and renal and secondary systemic changes.

If the onset is with prostatitis in early middle life scar tissue formation followed by adenomatous changes occurs, and symptoms of irritability precede those of obstruction. In this type, the scar tissue change is frequently the primary obstructing factor, associated or not with later adenomatous changes. The second classification includes those cases in which there are adenomatous changes with secondary infection induced by the blocked acini. In both types, the obstructive symptoms depend entirely on the shape and size of the obstruction and its location, particularly as to whether it is intra-urethral, at the internal sphincter or unusually intracystic. On account of this variability in location, rectal examination may give an erroneous idea of the size of the obstructing prostate; if located deep in the urethra, the prostate will seem much larger to the examining finger than if it were located high on the internal sphincter. As no two prostates were ever alike in size, shape, location, consistency and degree of infection,[1] the proper diagnosis in, and the method of handling, an individual case depends on determining its exact status in each of these particulars. For example, a small prostate with scar tissue and with a very small intra-urethral

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Read before the North Central Branch of the American Urological Association, St. Paul, Minn., Oct. 29, 1931.

1. Randall, Alexander: Surgical Pathology of Prostatic Obstruction, Baltimore, Williams & Wilkins Company, 1931.

adenomatous mass may block completely, while a large, intracystic, adenomatous prostate may be of little clinical importance, except for the associated infection.

From the standpoint under discussion here, cases of prostatic obstruction may be divided into those in which the obstruction gains control early in the course of the disease and those in which the wall of the bladder (by anatomic compensation) retains its ascendancy over the obstruction.[2] In the second type, the obstruction is imperfect and develops slowly, and the wall of the bladder compensates readily on relief of the acute dilatation. This accounts for the disappearance of a residual urine after catheterization in certain obstructed bladders. It is in this type, also, that diverticula[3] frequently develop. The first type is one in which the obstruction defeats the wall of the bladder early in the course of the disease. The more sudden the onset of the obstruction, the less the change in the wall up to the time relief becomes necessary. It is possible to classify the degree of change in the wall that has been brought about by the individual prostate, and as the bladder is the intermediary in renal damage and infection, one can determine best the most suitable individual treatment by studying alterations in the function of the wall of the bladder.

The first degree of change in the wall is a physiologic hypertrophy in which sensation is, to a certain extent, in direct ratio to intracystic pressure. In this type, on account of the increase in the initial force of the contraction, one expects some frequency and urgency of urination, with or without slightly diminished force of stream. Should an infection occur at this stage, it would be much more violent than in a normal bladder, owing to the trauma of the too forceful contraction of the wall of the bladder and its internal sphincter. Associated with this change in the wall of the bladder and progressing as it does, with the increased duration and type of obstruction and infection, comes increased strength and irritability of the internal sphincter. The trigonal muscle,[4] which lowers the floor in association with the action of the arcuate fibers, becomes hyperplastic in an attempt to depress the spastic, fibrous or adenomatous type of hindrance to the internal sphincter. The posterior urethra is elongated, made resistant to dilatation by the urinary stream and less mobile to the pump handle-like action given it by the anterior portion of the levator ani muscle.[5]

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2. Rose, D. K.: J. Urol. **26**:91, 1931; **27**:207, 1932.

3. Rose, D. K.: The Pathogenesis of Bladder Diverticula, Arch. Surg. **14**:554 (Feb.) 1927.

4. Wesson, M. B.: J. Urol. **4**:279, 1920. Young, H. H., and Wesson, M. B.: The Anatomy and Surgery of the Trigon, Arch. Surg. **3**:1 (July) 1921. Young, H. H., and Macht, D. I.: J. Pharmacol. & Exper. Therap. **22**:328, 1924.

5. Rose, D. K., and Deakin, Rogers: Surg., Gynec. & Obst. **46**:221, 1928.

The second degree of change produced by continued obstruction with increasing compensation is an early physiologic decompensation. At this point the obstruction is in the ascendancy in that it has continued its resistance past the point for which the wall of the bladder can compensate, and some residual urine has accumulated. This change is in the nature of a physiologic nerve block or pressure anesthesia,[6] a provision to deal with the increased intracystic pressure. The symptoms are now definitely those of obstruction, but a retention catheter even at this time, by increasing the irritability of the posterior urethra, emptying the bladder and so thickening the wall, can temporarily reduce or remove the residual urine. However, in certain types it may increase the block by traumatizing the obstructing surfaces. Such a situation would be most unfortunate, as any infection in the face of an increased block in the thickened wall tends to dissemination through the blood stream, directly up the ureteral [7] lumen or via the lymphatics.

The third degree is an early anatomic decompensation, that is, a beginning thinning of the peak of anatomic compensation of the wall. This is due to long-continued increase in capacity, fibrous tissue change and increased and continued pressure anesthesia. Decompensation may continue to cellule and diverticulum formation, and such a bladder, in the cystogram, often shows the typical conical allantoic weakness with cellules or diverticula and deep trabeculations about the base.[3] The symptoms of this degree are those of greater dysuria, the frequency and urgency either having passed, owing to the decompensated wall, or when persisting, causing very little distress. The amount of residual urine increases with decompensation.

The fourth and greatest degree of change in the wall of the bladder, myogenic decompensation, is the one in which there is a paradoxical incontinence; that is, all the elasticity of the wall has been lost. This may develop with or without associated infection. In a large majority of cases, infection has occurred, and its onset and progress may be traced by an analysis of the symptoms throughout the past years. It will usually be found that early in the course of the disease marked frequency, urgency, etc., developed and lasted for some time, indicating a sudden increase in irritability and so increased contraction and power of the wall of the bladder. A long-standing infection markedly increases the degree of decompensation.

The more sudden the onset of complete obstruction, the less marked, at the time, will be the change in the wall of the bladder, the infection and the damage to renal function. The more gradual the obstruction, the greater the change and the greater the percentage showing associ-

6. Reference deleted by the author.

7. Graves, R. C.: J. Urol. **18**:321, 1927. Gruber, C. M.: ibid. **23**:161, 1930.

ated pathologic conditions. The direct [8] or involuntary nerve reflex, the altered circulation, the type of ureteral orifice [7] the kink of the ureter over the vas deferens,[9] the descent of the base of the wall of the bladder,[9] the hypertrophy of the musculature closing off the intramural ureter,[10] all, in their influence on renal damage, are individual considerations in each type of obstruction, and all are associated with altered function of the wall of the bladder.

Cystometrograms that graph the changes in the wall of the bladder are presented in further explanation. The central nervous system was normal in all cases considered here.[11] While specific examples of the various stages of change are given, these cystometrograms can, in no way, represent other than the individual cases. But through an understanding of their interpretation on the basis of the interrelationship of pressure, capacity and sensation,[12] one can visualize the status of the wall of any bladder, that is, the mechanics bringing about local symptoms, as well as possible secondary general influences that may enter into the surgical handling of a specific case.

CYSTOMETROGRAM 1: "NORMAL"

Cystometrogram 1 shows a gradual increase in involuntary pressure with correctly placed sensations, and a moderately high voluntary pressure with good capacity and with a sphincter control in excess of requirements, as shown by the fact that there is no leakage about the catheter. The second curve is slightly higher and the capacity less than the first, which is characteristic of a great percentage of normal bladders and is due to stimulation of the smooth muscle by the rapid stretching and relaxation of the first filling.

CYSTOMETROGRAM 2: EARLY STAGE OF COMPENSATION (PHYSIOLOGIC HYPERTROPHY) OF WALL OF BLADDER

Cystometrogram 2 represents the first degree of change in an obstructed bladder in that the capacity is slightly decreased and the pressures raised, the initial involuntary contraction of the wall of the bladder being especially significant. Sensations remain normally placed. In a bladder showing an early compensation type of curve, one expects

8. Farrell, J. I.: J. Urol. **25**:47, 1931.

9. Tandler, Julius, and Zuckerkandl, Otto: Studien zur Anatomie und Klinik der Prostatahypertrophie, Berlin, Julius Springer, 1922.

10. Kreutzmann, H. A. R.: J. Urol. **19**:199, 1928.

11. Rose, D. K., and Deakin, Rogers: Am. J. Syph. **8**:371, 1929. Rose (footnote 2, second reference). Sachs, Ernest; Rose, D. K., and Kaplan, Abraham: Tumor of the Filum Terminale, with Cystometric Studies: Report of Two Cases, Arch. Neurol. & Psychiat. **24**:1133 (Dec.) 1930.

12. Rose, D. K.: Determination of Bladder Pressure with the Cystometer, J. A. M. A. **88**:151 (Jan. 15) 1927; in Graham, E. A.: Surgical Diagnosis, Philadelphia, W. B. Saunders Company, 1930, p. 803.

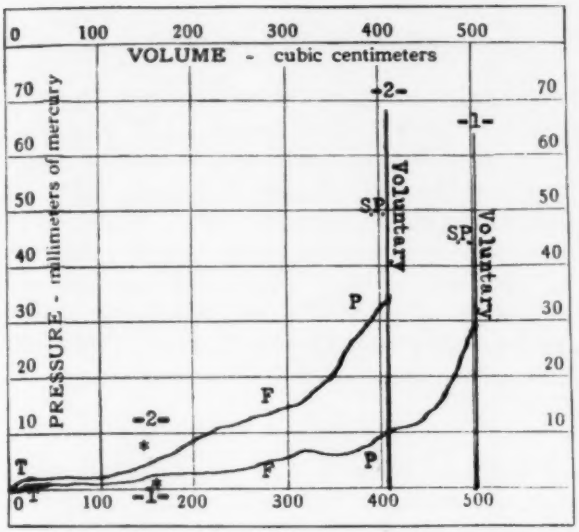

Chart 1.—Cystometrogram of a normal person (F). The terms abbreviated in this and subsequent charts are: Temperature (*T*); first desire to void (*); fulness (*F*); pain (*P*), and severe pain (*S.P.*). A gradual increase in involuntary pressure, correctly placed sensations and a moderately high voluntary pressure are shown. The patient had good capacity with a sphincter control in excess of requirements, as shown by the fact that there was no leakage about the catheter.

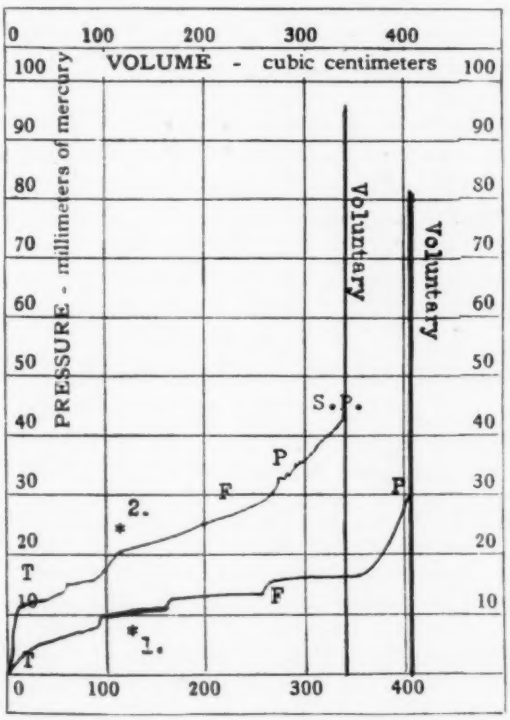

Chart 2.—Early stage of compensation of the wall of the bladder (patient F. S.)

some frequency and urgency, as, when the stimulation to void occurs, the contraction is more abrupt than normal. This abruptness is assisted reflexly by the irritability of the posterior urethra (pudic nerve).[13] Oscillations or toothlike variations in the smooth filling are caused by a transmission of the pump pressure through a fixed wall of the bladder, back to the mercury manometer.[14] They indicate, therefore, a spastic musculature. Infection without hypertrophy will not produce these oscillations. Normally, the musculature receives the inflowing fluid so smoothly that the pump pressure is absorbed by the elasticity of the wall of the bladder and not transmitted to the manometer.

CYSTOMETROGRAM 3A: ACUTE CYSTITIS

Cystometrogram 3A shows a very high voluntary and involuntary pressure, increased sensations with small capacity and no leakage. It is obvious that such a bladder would produce urgency, frequency and, probably, terminal pain and bleeding, that is, symptoms of irritation plus increased power. The increased power is due to the reflex contraction of the wall and the irritable mucosa resenting and expelling small amounts of fluid, which, by lessening the storage requirement, is a factor in producing greater frequency through greater contraction of the wall of the bladder by its diminishing capacity—a vicious circle. Should such a change occur in a markedly hypertrophic bladder, one can readily see why the residual urine would disappear and increased irritative symptoms supersede.

CYSTOMETROGRAM 3B: SUBACUTE URETHRITIS

In contrast with cystometrogram 3A, cystometrogram 3B shows urethritis without cystitis, low voluntary and involuntary pressure with increased irritability, and inhibition of the wall of the bladder protective to the hyperirritable urethra. In some instances, even a negative pressure is obtained, showing the psychic control over the involuntary wall of the bladder.[15] Leakage about the catheter is very unlikely to occur, even with severe pain of overdistention, which, characteristically, here occurs with a low pressure and small capacity. The same degree of pain in an acute cystitis occurring with an excessively high pressure and similar capacity would tend to show leakage about the catheter in a certain percentage of cases in the effort of the mucosa of the bladder

13. Barrington, F. W. F.: Proc. Roy. Soc. Med. (Sect. Urol.) **20**:22, 1927. Schwarz, O.: Ztschr. f. urol. Chir. **10**:167, 1922. Ranson, S. W.: The Anatomy of the Nervous System, ed. 3, Philadelphia, W. B. Saunders Company, 1927, p. 336. Learmouth, J. L., and Braasch, W. F.: Surg., Gynec. & Obst. **46**: 221, 1928.

14. Rose, D. K., and Rollins, P. R.: Pyelonephritis in Pregnancy: Its Treatment and Prevention Based on Cystometric Conclusions, J. A. M. A. **96**:235 (Jan. 24) 1931.

15. Rose (footnote 2, first reference).

to rid itself of the fluid. Such an inhibition may lower the pressure in a wall of known compensation and so markedly alter the picture (see cystometrogram 5). The influence of urethritis must therefore be borne in mind in the interpretation of all types of cystometrograms.

CYSTOMETROGAM 4: EARLY STAGE OF DECOMPENSATION (PHYSIOLOGIC) OF WALL OF BLADDER

Cystometrogram 4 shows a large capacity with low voluntary and involuntary pressure. The decreased sensations are physiologic, that is,

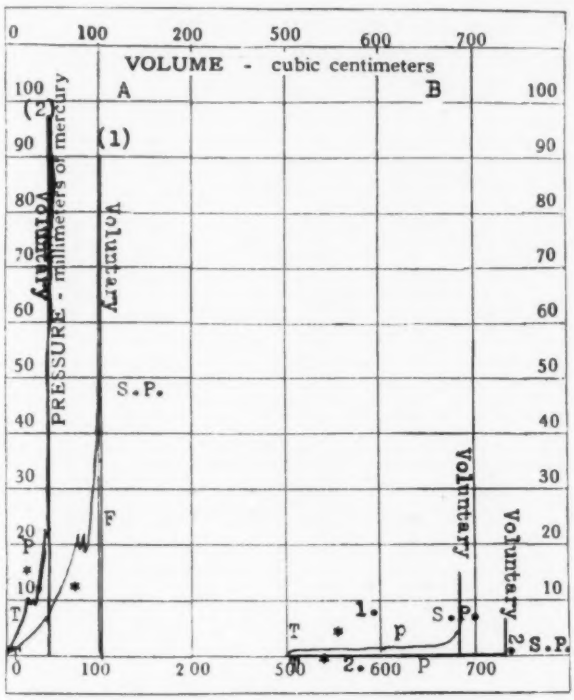

Chart 3.—*A*, acute cystitis (patient T. F.); *B*, subacute urethritis (patient F. F.).

of the pressure anesthesia type. At this early stage in the decompensation of the wall of the bladder, anatomic compensation is just below its peak. The patient, aged 50, carried 750 cc. of residual urine, which was not infected. His symptoms were those of marked obstruction without irritation. As he had never been catheterized, a catheter was attached to the manometer and the full bladder recorded 30 mm. of mercury (marked "A" on the chart). The bladder was then emptied, and cystometrogram 5 was made. "First desire to void" (*) in curve 1 occurred at 350 cc. and in curve 2 at 250 cc. (normal is about 150 cc.).

With this exception, the sensations of fulness and pain were normally placed for the type of curve. The occasional abrupt, single rises are due to the thickened wall, which contracts reflexly with the slight discomfort of the catheter. Note that the severe pain (*S. P.*) of overdistention does not occur up to 600 cc. filling. Taken as a whole, this cystometrogram shows a slightly weakened wall and yet one that is far from being thinned. Delayed "first desire to void" in association with a compensated wall accounts, in part, for the lower pressure and rather large capacity.

Following this cystometrogram, rather than put in a retention catheter, the patient was watched carefully and catheterized every six to eight hours. Twenty-four hours later cystometrogram 5 was made.

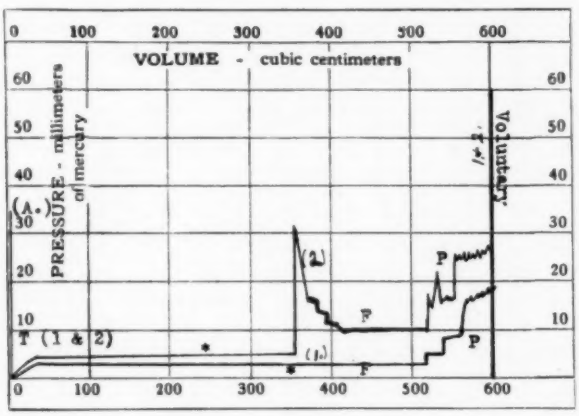

Chart 4.—Early stage of decompensation of the wall of the bladder (patient E. H. [×]). As this patient had never been catheterized, a catheter was attached to the manometer, and the full bladder recorded 30 mm. of mercury (marked *A*). The bladder was then emptied and the cystometrogram made.

CYSTOMETROGRAM 5: CATHETER COMPENSATION

As compared with cystometrogram 4, cystometrogram 5 immediately shows the effect of catheterization in the decreased capacity, much higher pressure, increased sensations and spasticity of the wall of the bladder, as shown by the oscillations in curve 2. A retention catheter, in this type of compensated wall, would produce a curve not unlike that of cystometrogram 3A, that is, a very abrupt rise, depending, of course, on the duration of the retention catheter and the associated infection. In this (5) one has, in curve 1, a low pressure following the base line to 170 cc., at which point an abrupt rise occurs. This is due, in part, to an associated urethritis, produced by the intermittent catheterization, temporarily inhibiting the wall of the bladder (see cystometrogram 3B). While the full bladder was emptied just before

making curve 1, its filling had been so gradual that the stimulating effect of a rapid stretching of the smooth muscle was absent, but this effect was produced by the first cystometric filling and explains the rather abrupt rise in pressure with the second filling, as well as the higher voluntary pressure. It is therefore a catheter compensation in an anatomically thickened wall associated with subacute urethritis produced by intermittent catheterization.

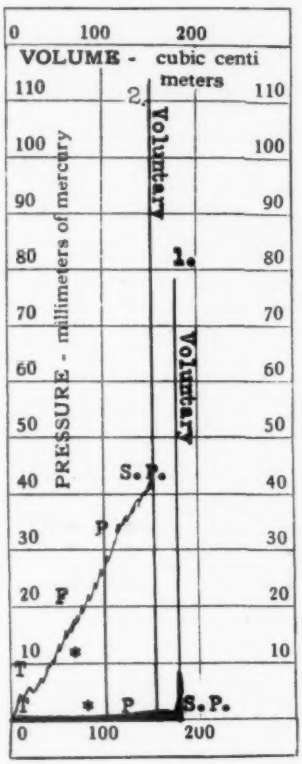

Chart 5.—Catheter compensation (patient E. H. [×]).

CYSTOMETROGRAM 6: ACUTE DECOMPENSATION OF WALL OF BLADDER

Cystometrogram 6 shows a large capacity and lowered voluntary and involuntary pressure, with slightly delayed sensations. The patient had retention of urine (1,300 cc. infected with Bacillus coli), enlargement of the prostate, with marked secondary anemia, and an inguinal hernia, which was a recent development in association with straining on urination. The second curve, being higher than the first, favors a normal central nervous system, which is an important point in considering such a large capacity of the bladder. Associated with this is

the interesting fact that his first failure to urinate occurred only a few hours before examination. Undoubtedly, from the history, an acute cystitis had developed three years previously, and, at that time, with irritation of the already thickened wall of the bladder, there had been periods of marked frequency, urgency with incontinence of urine, and some terminal pain with bleeding. This infection subsided, and the strength of the wall of the bladder started on its downward path once more, but it was still able to overcome the particular type of obstruction, only to fail in acute decompensation on the day the cystometrogram was done.

CYSTOMETROGRAM 7: LATE DECOMPENSATION OF WALL OF BLADDER

Cystometrogram 7 shows only one complete filling curve, the second being partial. Curve 1 shows normal or diminished capacity with

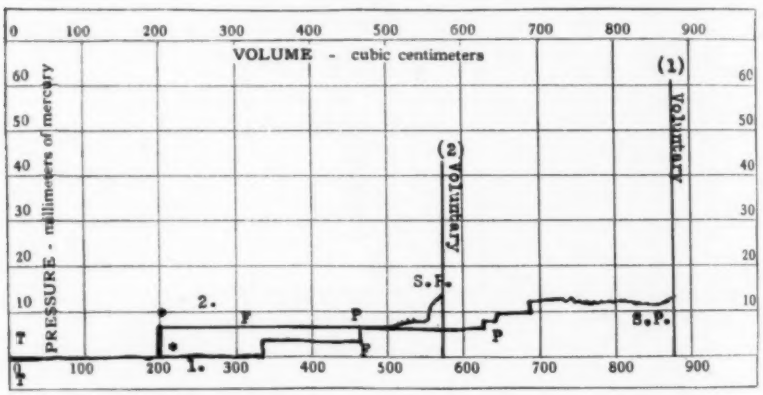

Chart 6.—Acute decompensation of the wall of the bladder (patient W. A. D.).

unusually high voluntary and involuntary pressure. The involuntary pressure is paradoxical, the effect of the catheter, in that it is abruptly high after an initial low pressure to 170 cc., with which there is no "first desire to void" (*). This initial low pressure indicates myogenic decompensation, and this is confirmed by curve 2. Sensations are delayed by prolonged pressure anesthesia influenced by chronic inflammatory changes. The patient had 400 cc. of residual urine, had been on self-catheterization and had been markedly infected (B. coli) for years. His symptoms were those of obstruction with moderate irritation when the bladder was markedly overdistended. Cystoscopic examination showed three large diverticula, coarse trabeculations and many shallow and a few ballooning cellules.[3] The prostate and diverticula were removed in a two stage suprapubic operation, with satisfactory results. The results of neurologic examinations both before and after operation were entirely negative.

Without catheterization this curve would have been entirely different, that is, it would have shown large capacity, lower pressure and greater delay in sensation (*). The initial flat curve with abrupt rise, delayed "first desire to void" with an oscillating type of involuntary pressure with high voluntary pressure, together with the long history of catheterization, acute blocks with relief, and a remaining residual of 400 cc., show the cystometrogram to be that of a late decompensation of the wall of the bladder with catheter influence.

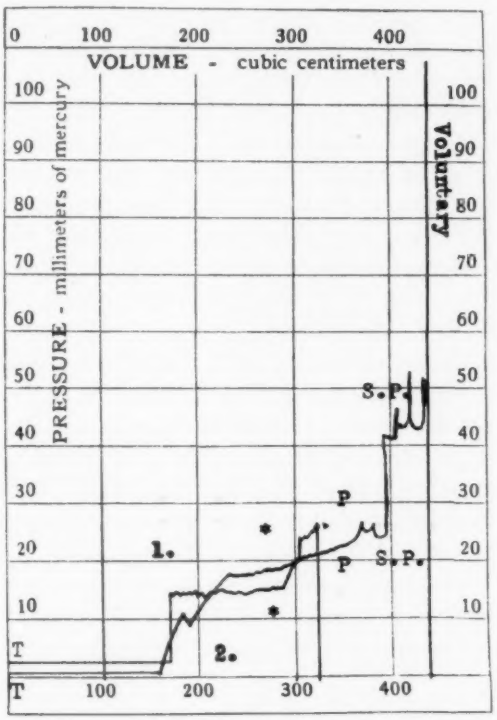

Chart 7.—Late decompensation of the wall of the bladder (patient J. G.).

SUMMARY WITH SURGICAL CONSIDERATIONS

Prostatic obstruction, therefore, brings about changes in the wall of the bladder depending on its size, shape, position, location, degree of infection and rapidity of development. These changes may be arrested at any stage of compensation or of decompensation provided the balance of power between prostatic resistance and expulsive force of the wall remains in favor of the latter. Compensation may be effected, depending on the degree of obstruction and decompensation, by means of a retention catheter or even, at times, by a single catheterization. An acute infection under similar conditions may bring about a compensation.

The surgical considerations are that a physiologically hypertrophied wall will attempt to force the retention catheter out and so cause pain, exacerbate and tend to generalize infection by trauma, and endanger the kidneys (infection or back pressure change).[10] If this trauma occurs and with it the compensated bladder wall is still unable to overcome the obstruction, the vicious circle of infection plus trauma without free drainage is initiated and continues to the point at which volume of fluid overcomes the forceful contraction of the wall. Catheterization is then increasingly dangerous.[16] The exception to bad results must be due, in these cases, to a sufficient drainage, to a low compensation in the wall of the bladder, or to the fact that the organisms are of low virulence. This degree of physiologic hypertrophy can be recognized clinically by the history of moderate obstructive symptoms with occasional complete obstruction, relieved by catheterization. In this, one must differentiate the obstruction of a distended wall (drinking too much, unable to void at an early warning, etc.) from one in which repeated early attempts to void were futile, with secondary, so to speak, dilatation thinning of the wall. In this type, from the standpoint of the influence of the wall of the bladder alone, absence of an acute or subacute infection indicates a one stage removal with free and uninterrupted drainage. The type of prostate that has led the bladder on to greater and greater compensation only to block suddenly is very likely to be one of mixed type with fibrous predominance located intra-urethrally, or one of large adenomatous type located either very high on the urethra or intracystically. As the former constitutes the larger class bringing about this change, and as it enucleates more easily without long drainage of the bladder, it does to this degree, favor the one stage operation in type. Gross pathologic classifications of benign conditions of the prostate (fibrous, mixed or adenomatous) have absolutely no individual constancy in the type of physiologic changes that they initiate or maintain. Similar mechanics of obstruction may be brought about by prostates of wide pathologic variance.

The two stage operation is favored in the face of marked decompensation of the wall of the bladder, as in this type drainage for relief is usually indicated, while the operative status of the patient is being determined. If this drainage is by urethral catheter, which is well borne in a decompensated wall, prostatic removal is indicated only after the infection associated with the catheter has subsided with continued suprapubic drainage.[17] These patients are easily recognized by the long history of dysuria and irritative symptoms at the time that they passed through their infection compensation, and later, decompensation to

16. Rose, D. K.: J. Missouri M. A. **29**:10 (Jan.) 1932.

17. Thomas, G. J.; Exley, E. W., and O'Brien, W. A.: J. Urol. **15**:343, 1931.

subsequent greater dysuria. They usually show evidence of chronic infection and reduced renal function.

Any type of obstructing prostate may bring about a marked degree of decompensation if there is no interference by an exploring cystoscope of urethral catheter. When there has been such interference, however, the logical subsequent course is one of chronic infection with a reduced residual urine, the amount of the reduction indicating the amount of catheter compensation of the wall of the bladder and furnishing an index to the ratio between the expulsive force of the wall and the prostatic resistance.

Nearly complete obstruction, with a very high level of nonprotein nitrogen in the blood and a long history of dysuria, means a decompensated bladder wall. When there is no infection, no matter how complete the decompensation, return will be rapid, and the retention urethral catheter will be poorly borne. On this basis, it is best to institute suprapubic drainage without cystoscopic examination or cystogram, that is, without urethral trauma, leaving such procedures until renal function has improved. In certain bladders handled in this manner there is, at the ultimate time of closure of the suprapubic wound, a rise of temperature due to a bacterial invasion of the kidney, the seminal vesicles or the blood stream. This, in turn, is due to the high intracystic voiding pressure, that is, a long-contracted and infected bladder, and to an apparent lack of resistance to the infection, as the patient, at no time, has been subjected to infection plus increased intracystic pressure or to urethral foreign body. If, therefore, with the beginning of voiding through the urethra, the temperature rises, it is essential that means be used to decrease the infection of the bladder, and, at times, it may be necessary to reopen the suprapubic wound for a few days by passing a very small, wax bougie through the granulating wound in order that this intracystic pressure phase of the vicious circle may be broken.

As for minor operative procedures for the relief of prostatic obstruction, such as the various forms of prostatic punch, if the obstruction cannot be reduced below the level over which the expulsive force of the wall of the bladder will remain in easy, complete and permanent ascendancy, all are contraindicated on application of the foregoing principles.

Beaumont Medical Building.

ETIOLOGY OF GALLSTONES

I. CHEMICAL FACTORS AND THE RÔLE OF THE GALLBLADDER

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RUDOLF SCHOENHEIMER, M.D.

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CHICAGO

The problem of cholesterol gallstone formation is essentially that of precipitation of cholesterol in the bile, because with remarkably few exceptions human gallstones are composed for the major part of cholesterol. This cholesterol may be of almost pure crystalline form or may be mixed with varying amounts of bile pigments or calcium, but the cholesterol-containing stones make up an enormous majority of all human gallstones, and according to Peel [1] the cholesterol content of mixed concrements averages at least 80 per cent. The only exceptions are the pigment stones or calcium carbonate stones. Such stones are quite rare in human beings, although they are common in animals. The entirely different composition of the two classes of stones, together with the fact that cholesterol stones are never found in animals, suggests the probability that they have an entirely different pathogenesis.

There are two problems to solve in the formation of cholesterol-containing gallstones: first, the means by which the cholesterol in the bile is precipitated and, second, the circumstances that are necessary to bring about sometimes typical stone formation with radial or concentric arrangement of crystals and at other times only single crystals. In the latter problem, the physical conditions of bile are of course important, and the time element is a great factor; we shall concern ourselves in this paper only with the first question. The consideration of the tiny pigment concretions studied by Naunyn,[2] Rovsing [3] and Rous [4]

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1. Peel, A. A. F.: Chemische Untersuchungen ueber Gallensteine und Galle, Ztschr. f. physiol. Chem. **167**:250, 1927.

2. Naunyn, B.: Cholelithiasis, Leipzig, F. C. W. Vogel, 1892.

3. Rovsing, T.: Pathogénie des calculs biliaires et indications opératoires, Paris, Masson & Cie, 1925.

4. Rous, P.: Physiological Factors in the Genesis of Gall Stones, Proc. Inst. Med., Chicago **1**:33, 1928.

and of their acting as nuclei about which cholesterol precipitates seems to us to be entirely beside the point. Even if they are found at the center of some calculi, a fact that Aschoff [5] denied, the obviously decisive point is that neither they nor any other particulate matter will cause the crystallization of cholesterol out of normal bile, and an explanation must be sought of what factors influence the bile to bring about a supersaturation of cholesterol.

Cholesterol stone formation is also distinctly a human problem, as such concretions are never found in animals but are peculiar to man. In the gallbladder of the ox as well as in that of numerous experimental animals, the formation of stones is quite common, but these stones invariably are composed of bile pigment together with more or less calcium, and they never contain more than the faintest traces of cholesterol. Such stones have been produced by an enormous number of means which cannot be reviewed here, but the main factor in their formation seems to be stasis with inspissation of the bile due to the absorption of water. We know of but one paper in which the authors have claimed the formation of experimental cholesterol stones. Recently Wilkie [6] reported cholesterol stone formation in the rabbit by infection introduced either directly into the gallbladder or by intravenous injection. He gave no facts as to the amount of cholesterol and no results of analysis for cholesterol. This exception, therefore, seems doubtful, to say the least, and merely serves to emphasize the particular human specificity of cholesterol gallstone formation.

In the earlier studies of cholesterol metabolism attempts were made to link it with the formation of gallstones. However, the greatest stumbling block has been that, although by feeding or parenteral injection of cholesterol the cholesterol content of the blood may be lifted to a high level and deposits of cholesterol laid down in the aorta, suprarenals, etc., there has never been produced by this means a significant elevation of the biliary cholesterol, nor has it been shown by any one that the biliary cholesterol bears the slightest relation to the blood cholesterol. The literature on this subject was reviewed by McMaster.[7] While the total output of cholesterol may possibly be influenced by diet, the experiments of Naunyn,[2] Jankau,[8] Thomas [9] and Lichtwitz [10]

5. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.
6. Wilkie, A. L.: The Bacteriology of Cholecystitis, Brit. J. Surg. **15**:450, 1928.
7. McMaster, P. D.: Studies on the Total Bile, J. Exper. Med. **40**:25, 1924.
8. Jankau, L.: Ueber Cholesterin und Kalkausscheidung mit der Galle, Arch. f. exper. Path. u. Pharmakol. **19**:237, 1892.
9. Thomas, quoted by McMaster (footnote 7).
10. Lichtwitz, L.: Ueber die Bildung der Harn und Gallensteine, Berlin, Julius Springer, 1914.

make it quite clear that the concentration of cholesterol in the bile remains the same even after feeding enormous amounts. McMaster [7] found a slight increase in the biliary cholesterol in dogs following diets high in cholesterol. The increase was not nearly as great, however, as that produced by starvation, and it represented only a very small fraction of the amount fed. For this reason all such attempts at the explanation of gallstones on the basis of hypercholesteremia have failed. These experiments also have led to numerous errors, as cholesterosis of the wall of the gallbladder is often observed after feeding experiments and is even found in many normal dogs. It has been assumed that this cholesterol is biliary in origin, when as a matter of fact further studies have shown that it is hematogenous in origin and that the biliary cholesterol remains normal.

At the outset of investigation, however, two points must be recognized. The first is the great difficulty of applying animal experiments to the human biliary system and the great likelihood of drawing false analogies, owing to fundamental differences in their behavior. In the bile of all animals that we have studied (ox, dog, rabbit, goat) the cholesterol content has been very low, indeed but a small fraction (from 10 to 20 per cent) of that of human bile. It is a common misapprehension that most of the cholesterol in the bowel is biliary in origin, whereas the overwhelming majority of it is excreted directly from the intestinal mucosa. Schoenheimer has shown that the colon,[11] jejunum and ileum [12] of dogs secrete very large amounts of sterol and that even the pancreatic juice [13] has about the same cholesterol content as bile. This will explain, therefore, the absence of cholesterol stones in animals, and no theory of human gallstone formation is valid unless it explains the absence of such a phenomenon in experimental animals.

The second important point is the insolubility of cholesterol in water which has been noted ever since its discovery. In the bile, however, it has been assumed, but never proved, that the substances that keep it in solution are the salts that occur in exceedingly high concentration in the bile (from 2 to 7 per cent). Solutions of bile salts have the power to dissolve surprisingly large amounts of this exceedingly insoluble substance. It is quite astonishing, therefore, that more work has not been done on this subject, as it so clearly must be related to the matter of gallstone formation. There are two kinds of bile acid known in human bile, cholic acid and desoxycholic acid, differing only in the number of hydroxyl groups (cholic acid contains three and desoxycholic

11. Schoenheimer, R., and von Behring, H.: Ueber die Exkretion gasältigter Sterine, Ztschr. f. physiol. Chem. **192**:102, 1930.

12. Schoenheimer, R.: Data not yet published.

13. Dr. L. R. Dragstedt supplied large amounts of pancreatic juice for these studies.

acid two groups). A third bile acid, lithocholic acid, occurs in such a small amount that its presence can be neglected. As all bile acids are present in combined form with either glycocoll or taurine, four conjugated bile acids are important in human bile, glycocholic and taurocholic acid and glycodesoxycholic and taurodesoxycholic acid, all of which have more or less different physical and chemical properties. It has always been assumed that the simple uncombined acids are never found in bile. This matter will be discussed more fully in a later paper.

Thus far no quantitative method has been devised for the estimation of simple unconjugated bile acids. The combined bile acids can be accurately measured by the determination of the aminonitrogen in the bile by the Van Slyke [14] gas analysis method, as each molecule of either taurocholic or glycocholic acid contains one molecule of combined aminonitrogen (Schmidt and Dart [15]). A preliminary determination of aminonitrogen is made, as the bile contains small amounts of substances containing free amino groups. Then the bile is hydrolyzed at a pressure of 20 pounds in the autoclave for five hours in 8 per cent sodium potassium hydroxide, thus freeing the amino-acids in the combined bile acid. From the difference between the two readings one can readily calculate the bile acid content. On account of the large amount of substances present in the bile besides bile acids that react to the Pettenkofer tests (fatty acids, etc.), we do not feel that the quantitative Pettenkofer method is specific enough for use in the bile.

There are some difficulties in completely separating bile acids and cholesterol as they occur in human bile. This is evidenced by the fact that most commercial preparations of conjugated bile acids contain appreciable amounts of cholesterol in spite of the fact that attempts have been made to separate the two substances. The bile acids have the power to hold in solution numerous other ordinarily insoluble substances, especially those of a fatty nature. This can be shown crudely very simply by adding bile to milk. The latter immediately becomes clear and transparent owing to the dissolving of the fat droplets in the bile acid solvent, and fat droplets can no longer be seen under the microscope. Recently a similar rôle was ascribed by Walsh and Ivy [16] to the fatty acids that are present as soaps in the alkaline bile. To us this seems exceedingly doubtful. The amounts of fatty acids present in the bile are much too small to hold in solution as much cholesterol as is found in human bile. The bile acid content of the latter is quite

14. Van Slyke, D. R.: The Quantitative Determination of Aliphatic Amino Groups, J. Biol. Chem. **12**:275, 1912.

15. Schmidt, L. W., and Dart, A. E.: The Estimation of Bile Acids in the Bile, J. Biol. Chem. **45**:145, 1920.

16. Walsh, E. L., and Ivy, A. C.: Observations on the Etiology of Gall Stones, Ann. Int. Med. **4**:134, 1930.

high and varies between 2 and 7 per cent, while the proportion of fatty acids is only a very small fraction of 1 per cent, an amount not nearly sufficient to dissolve any considerable percentage of the cholesterol. The determination of fatty acids in bile is extraordinarily difficult because these substances can be separated from the bile acids only with the greatest difficulty, as when acid bile is extracted with organic solvents, large amounts of bile acids as well as fatty acids are removed. Therefore, the standard methods used to determine fatty acids in blood or tissues are not applicable to the bile. Ivy determined the saponifiable material in bile in the expectation of arriving at an approximate estimation of the fatty acid content. It is obvious, therefore, that in his experiments the bile acids and fatty acids were not separated, and what he considered as saponifiable substances were really a mixture of fatty acids with overwhelming amounts of bile acids.

In our experiments it was attempted to investigate which of the various bile acids were responsible for the solubility of the cholesterol in the bile. The previous work of Wieland and Sorge [17] on the so-called choleinic acids seemed to give a key to the problem. Choleinic acid had formerly been considered to be a distinct bile acid, but these authors were able to show that it is a relatively loose chemical compound of desoxycholic acid with a mixture of fatty acids. These "addition compounds" of fatty acids and bile acids are comparatively stable substances. It is by this means that desoxycholic acid has the power to render soluble various ordinarily insoluble fatty acids. It was also shown that desoxycholic acid is able to make such addition compounds not only with the fatty acids but with numerous other substances ordinarily insoluble in water, in spite of the fact that they contain an insoluble fraction.

It can be seen from the results of the following experiments that cholesterol may be held in solution in the bile in a similar addition compound not only with desoxycholic acid but with all the other bile acids as well.

Theoretically, if the cholesterol in the bile is held in combination with the bile salts, precipitation of the cholesterol should occur if the bile salts are removed from the solution by any means. Throughout our experiments this was always actually the case. Part of the bile acids are insoluble in water, and if bile is acidified the soluble salts of the bile acids are changed into the insoluble acids which are precipitated. Such a precipitate always contains large amounts of cholesterol.

The following series of experiments in which the various bile acids are precipitated in rotation by specific substances indicates that each of

17. Wieland, H., and Sorge, H.: Untersuchungen ueber die Gallensaüren, Ztschr. f. physiol. Chem. **97**:1, 1916.

the fractions carries with it part of the cholesterol. Human bile, after deproteinization, was treated with iron chloride. This precipitates most of the glycocholic acid and glycodesoxycholic and taurodesoxycholic acid. Lead acetate may also be used for this purpose. The precipitate was treated with sodium carbonate to reform the soluble sodium salts. The salts were then dissolved in alcohol, and digitonin was added. There was a typical precipitate of the insoluble cholesterol digitonid. However, after the removal of the heavy metal precipitate, the bile still contains some cholesterol while held in solution by the remaining bile acids which are not precipitated by the heavy metals. Most of these remaining bile acids, mainly taurocholic acid, may be salted out of the solution by saturation with sodium chloride or ammonium sulphate. This fraction of taurocholic acid, if redissolved in alcohol, may be demonstrated to contain cholesterol also by the digitonin method. The difficulties of isolating the entire series of bile acids quantitatively from human bile are, with the present knowledge, practically insuperable, and considerable amounts of them are lost in purification by recrystallization or other chemical means. However, it was finally possible to secure fractions that consisted practically of a single kind of bile acid and a lesser amount of cholesterol. The cholesterol content of these complexes was from 6 to 8 per cent, and in spite of this high content of insoluble cholesterol they would all dissolve readily in water, giving perfectly clear solutions. The results of these experiments indicate that not only the salts of the desoxycholic acids but also those of the other bile acids are able to form with cholesterol complexes similar to the addition compounds of Wieland and Sorge.[16]

In order to study the properties of these complexes more accurately, attempts at synthetic preparation of the various complexes were carried out in the following manner: The pure sodium salt of the bile acid was heated in alcohol solution with an excess of cholesterol, and the alcohol was then completely evaporated off in a water bath. The residue was boiled for several hours with twenty volumes of water under a reflex condenser, and the excess cholesterol was thus gathered in large masses and could easily be filtered off. The remaining clear, watery solution was then evaporated to dryness.[18] These further purified substances are very easily soluble in water, giving a perfectly clear solution, and correspond in all their physical and chemical properties to the complexes that had been isolated from the bile. Such complexes of cholesterol and bile salts are all soluble in water, but are all insoluble in the acid form, the only exception being taurocholic acid, which is

18. The further purification of these substances was carried out in different ways according to the type of bile acids used. These purely chemical data are being reported elsewhere.

soluble in acid as well as in alkali. This exception in the case of taurocholic acid has considerable clinical interest, as it is theoretically possible at least that by this means the cholesterol in the bile would be protected in its solubility against changes in the acidity of the bile, and in view of the great excess of bile acids, taurocholic acid alone would have the power in most cases to hold the cholesterol in solution.

It appears, then, that the complexes isolated from the bile and those prepared synthetically are identical. The stability of the union in this complex is in most cases loose, but the desoxycholic acid complex is considerably more firmly bound together. The complexes derived from glycocholic and cholic acids are considerably less stable than the others, and although they are stable in solution, in the dried form they tend to separate into their components. The addition of organic solvent permanently breaks up the complex, at least in part, almost certainly owing to the fact that these solvents themselves displace the cholesterol and enter into similar complexes with the bile acids. Xylene and ether for example, both have this property. As was mentioned, digitonin will precipitate the cholesterol from a solution of the complex.

One of the most interesting studies made, and one that has an obvious clinical application, is the experiments with a dialyzing membrane. Bile acids are easily dialyzable, and experiments were made to see if, as they pass through a membrane, they would carry the cholesterol in solution with them. Solutions of various complexes, 5 per cent in strength, were dialyzed in a parchment membrane against water. After from four to twenty-four hours, it was noted that the solution in the membrane, which had been perfectly clear, had become cloudy. Microscopic and chemical tests showed that this turbidity was due to the precipitate of amorphous or crystallized cholesterol, and that the fluid outside the membrane contained bile acids but no cholesterol. It was obvious that the bile acids, by leaving the membrane, had so reduced the bile acid content within, that there was not sufficient solvent left to hold the cholesterol in solution and it was therefore precipitated. In studying our pure synthetically prepared complexes in this manner, this same phenomenon was observed throughout the series, with the exception of desoxycholic acid and taurocholic acid. These groups appeared to have the power to make a firmer union with the cholesterol, and separation by dialysis could not take place. This phenomenon occurs not only in the synthetically prepared products, but can be demonstrated in human gallbladder bile very simply; if the latter is dialyzed against water, the bile soon becomes turbid with cholesterol, and large amounts of bile acids can be found outside the membrane. With bile acid fractions from the dog or ox this phenomenon is much less marked; the dialysis must be prolonged until the extraction of

bile acids is almost complete, and even then but a very slight turbidity will appear because of the minute amounts of cholesterol in these substances.

Similar experiments for other purposes have been carried on by Verzar.[19] He brought cholesterol into aqueous solution by pouring a 10 per cent solution of cholesterol into a 5 per cent aqueous solution of bile salts. This solution, which still contained alcohol, was dialyzed against a 5 per cent solution of the same bile salt without cholesterol (and alcohol?). After a certain time, using the very sensitive Salkowski reaction, he found cholesterol outside the membrane and believed that the bile acids had made the cholesterol dialyzable. As we did not believe his conclusions, we repeated the experiment, using not a solution containing alcohol, as Verzar did, but the complex of sodium glycocholate with cholesterol which, as has been mentioned, is very easily water-soluble. Outside the membrane was a 5 per cent solution of sodium glycocholate, which was previously purified, because most preparations of this substance on the market contain more or less cholesterol. We could not find the smallest traces of cholesterol outside the membrane after dialysis for twenty-four and forty-eight hours. The results of Verzar can be explained by the fact that he dialyzed alcoholic solutions against watery solutions. Also he did not mention whether the sodium glycocholate outside the membrane was purified to remove the last traces of cholesterol which could have given the Salkowski reaction.

The problem as to whether these complexes isolated from the bile that were synthetically prepared are actual addition compounds or whether they represent simply a phenomenon of common solubility cannot be answered as yet, as further work is necessary involving crystallographic studies, molecular weights, optical rotation studies, etc. It is certain, however, that at least the desoxycholic acid-cholesterol complex appears to be a definite chemical compound. In the human bile, therefore, part of the cholesterol is firmly bound and another part is more loosely bound. The investigation of the properties of these individual substances is being further continued. It is obvious from the data presented that the maintenance of the cholesterol in solution in the bile is dependent on its bile acid content. As soon as the bile acid content falls below a certain level the cholesterol is precipitated, with the obvious implication of possible formation of gallstones. From our experiments in the preparation of synthetic addition compounds, as well as from actual studies of the bile itself, it appears that this critical level is reached when the bile salt-cholesterol ratio reaches about the level of 13, and if it falls below this level precipitation will occur. In human

19. Verzar, F., and Kuthy, A.: Die physiologische Bedeutung der Hydrotropie, Biochem. Ztschr. **225**:267, 1930.

bile the average bile salt-cholesterol ratio is 20 : 30, and it is obvious that this is dangerously near the critical point and that a relatively slight disturbance will bring about precipitation.

In the animals thus far studied (goats, rabbits, cattle and dogs), while the bile salt content approximates that of human bile, the cholesterol content is very small, so that the ratio is much higher than in human bile, generally about 100. It is clear, therefore, that in animals there is a wide range in which variations in the ratio may occur without coming near the danger point, and one can see why cholesterol gallstones never occur in animals nor can be produced experimentally, while in the human being gallstones are predominantly made of cholesterol.

After recognizing the importance of the bile salt-cholesterol ratio for the formation of gallstones, one can theoretically see two possibilities of its application to clinical disease, the first being a differential absorption of the two substances by the mucosa of the gallbladder in the process of concentrating the bile, and the second, the excretion by the liver of bile containing so low a proportion of bile salts that they could not hold the cholesterol in solution. The experiments reported in this paper were undertaken in order to study the rôle of the absorptive mechanism in the gallbladder as a factor in changing the bile salt-cholesterol ratio.

EXPERIMENTATION

The first step was to determine the action of the normal gallbladder in its concentration of the bile. This was done in the following manner. It was assumed that thirty-six hours' starvation was the maximum that could occur under physiologic conditions. Also it is well known from the work of other students that the maximum or nearly maximum concentration of the bile occurred in about that period. Therefore, the animals were starved for that thirty-six hours so that no gallbladder contractions would occur, and at the end of that time they were anesthetized with barbital, the abdomen was opened, the cystic duct was clamped at once to prevent further escape of bile, and the common duct was cannulized. After sufficient liver bile had been secured for analysis, the animals were killed by electrocution and the gallbladder bile and concurrently secreted liver bile were analyzed. This was assumed to show the normal action of the gallbladder mucosa.

The results of these analyses are shown in table 1. The concentration of the bile in the gallbladder as measured by us in this as well as in numerous other experiments using the bile salts and cholesterol as indexes is from three to ten times that of the liver bile, most of the figures lying distinctly in the lower half of the range. The higher values are generally due to the concentration by the gallbladder of

rather dilute bile which is often concentrated to the same levels in the gallbladder as are the thicker biles. There seems to be a rough limit beyond which the normal gallbladder in dogs does not go, even if it starts with very thick bile. This is represented by the level of about 25 per cent total solids. When total solids are used as an index of the concentrating power of the gallbladder, it must of course be remembered that while water and salts are absorbed, considerable amounts of protein are excreted, mucus by the normal gallbladder and serum proteins as well by the inflamed viscus. We have not used bilirubin as an index of concentration in any of our work on account of the extremely fluctuant results obtained under certain conditions. For instance, Drury [20] once found a concentration of fifty-eight times the bilirubin in the liver, and on several other occasions almost equally high figures.

TABLE 1.—*Concentration of Bile by Normal Gallbladder. Simultaneous Estimation of Gallbladder and Liver Bile in Starving Dogs*

	Total Solids		Calcium		Cholesterol		Bile Salts		Ratio Bile Salts to Cholesterol	
Dog	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile	Gall-bladder Bile	Liver Bile
654	25.88	12.19	54.6	14.3	74	20	5,697	1,935	80	96
671	24.15	4.3	52.7	10.0	65	16	5,885	747	90	48
677	25.27	5.7	66.4	16.1	90	18	6,385	1,322	72	76
696	23.10	7.1	56.6	15.8	60	15	5,515	1,657	92	116
704	23.44	4.97	56.0	11.3	54	21	4,562	407	92	20
Average	22.04	6.4	57.2	13.5	68	18	5,610	1,214	85	71
Concentration	3.4 times		4.2 times		3.7 times		4.6 times			

This is obviously an impossible figure, as the biliary constituents are not soluble to anywhere near such a degree. The method of estimation of bilirubin is colorimetric, and, as he suggested, the marked acidification of the bile in the gallbladder may cause changes in the pigments that render the colorimetric estimation inaccurate.

However, whatever index is used, it can readily be seen that there is no lowering in the bile salt-cholesterol ratio by the normal gallbladder (table 1). While the gallbladder bile is from three to four times as concentrated as the liver bile, the figures show that in relation to the cholesterol content the bile salt content certainly does not fall. The average concentration of the cholesterol is 3.7 times that in the liver, while the average concentration of bile salts is 4.6 times. The average bile salt-cholesterol ratio is 71 in the liver bile and 85 in the gallbladder

20. Drury, D. R.: Studies on Total Bile: VIII. Conditions Influencing Calcium Content of Bile, J. Exper. Med. **40**:797, 1924. Drury, D. R.; McMaster, P. D., and Rous, P.: Observations on Some Causes of Gall Stone Formation, ibid. **39**:403, 1924.

bile. These figures in our opinion lie well within the margin of experimental error, which is considerable in the colorimetric cholesterol estimations. On account of the small size of many of the samples, the more accurate digitonin method could not be used. One is not warranted, therefore, in assuming that there is any differential absorption of the two substances by the normal gallbladder. This agrees with the commonly accepted hypothesis that the normal gallbladder absorbs only water and inorganic salts.

The action of the abnormal gallbladder was studied in a different manner. A series of dogs were anesthetized, the abdomen was opened, and the cystic duct was tied, care being taken not to injure the cystic artery. The gallbladder was then aspirated with a large needle and half of the contents was saved for analysis and the other half reinjected into the gallbladder and left there for twenty-four hours, at the end of which time the dog was killed and the two specimens of bile were compared.

In a previous paper [21] it was shown that the gallbladders of dogs treated in this manner promptly underwent severe degenerative changes, owing to infection arising in the stagnant and traumatized gallbladder. The bile, which is sterile in such animals, promptly becomes infected by a great number of organisms which can be demonstrated either by culture or smear. Microscopic section of the wall of the gallbladder shows that there is a marked onset of a moderately severe inflammatory process. As a matter of fact, microscopic section is hardly necessary, because the majority of the gallbladders treated in this manner appear whitish and grossly thickened, and there are more or less denudation of the mucosa and ulceration. Part of the dogs in this series were also subjected to the additional trauma of curettement of the inside of the gallbladder through a small hole. The holes in the gallbladder, whether for the large needle or for the curet, were closed by ligation, and the thickening and inflammation in the region of the ligature were especially marked. There can be no doubt, therefore, that we were dealing in this series of experiments not only with the factor of the stasis of the bile but with the factor of an obstructive pathologic condition in the gallbladder. In fact, it is very difficult, as was noted in our previous publication, to produce stasis of any sort without prompt onset of sepsis.

The results of the analysis of the action of the abnormal gallbladder are shown in table 2 and afford a striking proof of the differential absorption of the cholesterol and bile acids by such a viscus. Throughout the series there was a constant rise in the cholesterol content, accompanied by an equally constant fall in the bile acids. The average was

21. Andrews, E., and Hrdina, L.: Hepatogenous Cholecystitis, Proc. Soc. Exper. Biol. & Med. **28**:116, 1930.

a 28 per cent fall in the bile acids and a 29 per cent rise in the cholesterol, so that in the entire series the bile acid-cholesterol ratio of the controls was 97 and in the experimental series only 59. A study of the total solids in the bile shows that during the period of the experiment there was an average concentration of the bile of 10 per cent, so that these figures become still more striking, there being about a 40 per cent change in the bile acid-cholesterol ratio. The apparent rise in the cholesterol content in these series might be thought to be indicative of an excretion of cholesterol by the gallbladder, and the results of these

TABLE 2.—*Concentration of Bile by the Abnormal Gallbladder. The Cystic Duct was Tied, a Specimen was Aspirated from the Gallbladder, the Needle Hole was Ligated, and Twenty-Four Hours Later the Animals Were Sacrificed and a Second Chemical Analysis of the Gallbladder Bile was Made*

	Total Solids		Bile Acids		Cholesterol, Mg. per 100 Cc.		Change, per Cent		Ratio Bile Salts to Cholesterol	
Dog	Normal	Experimental	Normal	Experimental	Normal	Experimental	Bile Salts	Cholesterol	Normal	Experimental
859	.....	.....	6,040	5,327	54	58	—12	+ 6	112	92
885	.....	.....	4,600	1,880	48	58	—59	+20	96	32
889	.....	.....	6,010	3,910	45	70	—35	+49	131	55
892	.....	.....	4,862	4,647	40	47	— 5	+17	121	99
955	0.2320	0.2129	5,272	3,552	38	45	—33	+18	139	79
960	0.2130	0.3023	5,312	4,843	55	67	— 9	+23	97	72
961	0.2371	0.2516	5,572	3,260	56	77	—42	+37	99	43
962	0.2086	0.2662	5,705	2,512	49	71	—56	+42	117	35
923*	0.2245	0.3040	3,222	2,735	80	54	—15	—33	30	51
966	0.2930	0.2611	4,962	4,747	52	78	— 5	+50	94	61
968	0.2267	0.2539	4,615	3,755	50	54	—19	+ 9	92	69
18	0.1808	0.2514	5,827	5,765	50	64	— 3	+26	116	90
19	0.2256	0.1690	4,575	2,027	55	57	—69	+ 2	83	36
881†	0.2307	0.2567	3,352	.....	66	121	....	+83	51	..
883†	0.2050	0.2575	4,245	1,930	50	94	—55	+85	105	20
887†	0.2362	0.2791	4,825	4,595	68	79	— 5	+16	71	58
Aver.	0.2267	0.2554	.....	.....	..	..	—28	+29	97	59

* Pregnant dog. No explanation can be offered of the curious fact that this is the only negative change in the entire series.

† Gallbladder curetted.

experiments are typical of some work reported by other observers and interpreted in this manner. However, when one realizes the small amount of cholesterol in the bile of a dog (from 10 to 20 mg. per hundred cubic centimeters) and the high cholesterol content of the blood of the dog (from 200 to 300 mg. per hundred cubic centimeters), it is obvious that the results secured are no proof whatsoever of the secretion of cholesterol by the gallbladder wall, as the leakage of only two drops of blood or serum would more than account for the rise in the cholesterol. In the presence of frank infection, such as occurs in these cases, there is always a rise in the leukocytes in the bile, which will autolyze, and as leukocytes contain nearly 0.5 per cent of cholesterol,

the rise could be accounted for easily on this basis. It is obvious, however, that the diseased gallbladder acts exactly as the dialyzing membrane described in the earlier part of the paper, and that through its inflamed or denuded wall the bile acids will pass and the cholesterol will remain behind. It is clear that if this process continues very long in man, in whom the bile acid-cholesterol ratio is from 20 to 30, instead of about 100 as in the dog, it is possible to reach the critical point of precipitation of cholesterol within twenty-four hours after the reaction produced at the same rate as in the dog's bladder, and that this phenomenon is ample to account for the formation of cholesterol gallstones. If the bile salt-cholesterol ratio is at the level of 20 in the normal man and can be lowered 40 per cent in twenty-four hours, as occurs in the

TABLE 3.—*Human Gallbladder Bile in Cholelithiasis* *

Case	Cholesterol	Bile Salts	Ratio Bile Salts to Cholesterol
34963	69	1,130	17.0
32259	78	175	2.2
3971	138	1,302	8.8
33293	114†	0	0
35567	138	272	2.0
34904	188	1,310	7.0
35861	96	735	7.6
37847	282†	0	0
12869	360	45	0.12
38517	38	622	17.0
38764	15†	0	0
37714	128	344	2.6
Average	136	497	3.7
Mixed bladder bile from 30 postmortem cases of stones	400	247	0.6

* The bile salt-cholesterol ratio in normal human gallbladders is 20:40.
† Bile contained cholesterol crystals.

dog's gallbladder under relatively slight conditions of infection, one would be exactly at the critical point of precipitation, about 13.

If our theory of gallstone formation is true, one would expect to find in the human stone-containing gallbladders a much lower bile acid-cholesterol ratio than in the normal gallbladder. While the actual percentage of cholesterol itself is not important, the presence of sufficient bile salts to hold it in solution is the crucial point. Previous studies of this sort have been made by Newman [22] who analyzed the gallbladder bile in a long series of autopsies on bladders with and without stones. He reported that the cases with cholesterol-containing stones or cholesterol crystals showed a higher bile acid-cholesterol ratio than was found in the normal gallbladders or in those containing pigment or calcium

22. Neuman, C. E.: Beiträge zum Studium der Gallenniederschlags und Gallensteinsbildung, Beitr. z. path. Anat. u. z. allg. Path. **86**:187, 1931.

stones. We have analyzed the mixed gallbladder bile in a postmortem series of 30 stone-containing gallbladders.[23] Our observations in the postmortem cases confirmed those of Newman; the cholesterol content was 400 and the bile salt content 247 mg. per hundred cubic centimeters, the former figure being about normal and the latter only about one twentieth of the normal gallbladder content of bile acid. The average bile salt-cholesterol ratio in our series was 0.6, which offers a very striking contrast to the normal figures of from 20 to 30.

We have extended these studies to include fresh operative material. The gallbladder contents in twelve cases of cholesterol stones removed at operation were studied. As can be seen in table 3, the cholesterol content of this bile was quite within the normal range, but the bile salt was only about 10 per cent of the amount to be expected in the normal human gallbladder, while the average bile salt-cholesterol ratio was 3.7, representing a marked lowering of the normal bile salts and only a small fraction of the usual content. It is very difficult to get normal figures as to the normal gallbladder content in the human being as most of our analyses have been from postmortem material. However, the figures generally given are from 6 to 8 per cent of bile acids. Hammersten analyzed the bile in two cases of accidental death, and his analysis shows a bile salt-cholesterol ratio of about 40, the bile acid content being 8.2 and 8.7, respectively. These figures agree fairly well with the results of the series of analyses of normal human gallbladder bile made by Neuman. It is further interesting to note that in our series there were three cases of complete prolonged obstruction of the cystic duct, as shown by failure to visualize the gallbladder over a long period of time. In all of these cases there was a total absence of bile acid in the gallbladder bile, and in each case the cholesterol in the bile was precipitated and was in the form of a crystalline suspension. This may be regarded as a further proof of differential absorption of the biliary constituents in the abnormal gallbladder.

SUMMARY

1. The cholesterol is held in solution in the bile in a series of loose and firm chemical complexes with the bile salts.

2. Most of these complexes may be broken up by relatively slight influences, as for instance, by dialysis.

3. If the bile salts are removed from these complexes or from bile by any means, cholesterol is precipitated.

4. There is no differential absorption of cholesterol and bile salts by the normal gallbladder.

23. This material was kindly furnished to us by Dr. R. H. Jaffe from the Cook County Hospital, Chicago.

5. The infected gallbladder absorbs bile salts rapidly, but cholesterol very slowly, if at all.

6. Therefore, the bile salt-cholesterol ratio is of supreme importance in the precipitation of cholesterol from the bile.

7. The low bile acid content of the cholesterol stone-containing gallbladder bile from autopsy material, as reported by Neuman, is confirmed and extended to fresh operating room material.

CONCLUSION

Cholesterol precipitation from the bile, with its implication of gallstone formation, is caused by a lowering of the bile salt content of the bile.[24]

NOTE.—Since this paper was written attention has been called to an article of Elman and Graham (The Pathogenesis of the "Strawberry" Gallbladder [Cholesterosis of the Gallbladder], ARCH. SURG. **24**:14 [Jan.] 1932), in which our work was quoted in support of the theory that cholesterol is excreted by the mucosa of the gallbladder. This confusion was probably caused by the fact that in the preliminary report of this work our tables were omitted, but it is clear from tables 1 and 2 that although the cholesterol may be in a higher concentration, this fact is nullified by the corresponding inspissation of the bile as evidenced by total solids. We do not believe that the gallbladder mucosal secretion is a factor in gallstone formation; this feature has been discussed in a subsequent article (Andrews, E.; Hrdina, L., and Dostal, L. E.: Studies on the Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, ARCH. SURG., to be published).

24. It has been found that the cholesterol in pancreatic juice is removed by the Berkefeld filter and is therefore presumably not in the form of a solution.

FORTY-EIGHTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from page 614)

MISCELLANEOUS

Osteosclerosis Fragilitas.—Windholz [20] reported a case of generalized osteosclerosis fragilitas, marble-bone disease, in a 11 month old child. The bones were particularly rich in calcium, and no marrow cavity was demonstrable. All of the bones were equally involved. Banded transverse shadows were present in the metaphyseal regions. No fractures were demonstrable. There was periosteal new bone formation. A bilateral optic atrophy was present. There was a family history of inbreeding. The author mentioned that in the other cases of marble-bone disease reported in the literature consanguinity was a frequent finding. Fractures were common, presumably because of the decrease in the relative proportion of connective tissue in the bone, hence the name fragilitas. Atrophy of the optic nerve usually occurred due to the narrowing of the foramen of the orbit. Periosteal changes comparable in appearance were observed in some leukemias and ergosterol poisoning. Alterations in the blood picture were frequently observed. No etiology was known, although a disturbance in the glands of internal secretion had been suggested.

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20. Windholz, F.: Ztschr. f. Kinderh. **51**:708, 1931.

Callus Formation of the Tibia Without Fracture.—Ollonqvist [21] described a new disease of the inner aspect of the tibia. It consisted of a localized osteoperiostitis of the inner aspect of the tibial shaft, demonstrable roentgenologically and histologically. In all, sixty cases were seen, mostly in young recruits of about 20 years of age. Gradually, on assuming military service, local pain appeared. Early roentgenograms were negative. A deposit of smooth callus began to appear slowly, which after three or four months was easily visible. In from two to four months more, symptoms had disappeared. The author believed that the lesion was due to the traumas of impact, somewhat as in the case of "March-foot." Bacteriologically studied, the excised specimens were sterile. There was no syphilis. Ten excisions were performed.

[ED. NOTE.—This is an interesting entity. The causative mechanism is not yet clear.]

Pellegrini-Stieda's disease, or calcification of the internal lateral ligament of the knee, was believed by Rouillard and Bousser [22] to be a clinical entity. It occurred in adults, usually males, following trauma. Injury might be slight but more often was severe, either direct or indirect trauma. At first the symptoms were those of any knee injury. There was then a period of improvement but never complete recovery. After weeks or months, disturbance of function and pain increased until they reached a point at which they were stationary. Motion was limited. There was tenderness over the internal condyle and often the condyle appeared hypertrophied. Roentgenograms were essential for diagnosis. They showed a shadow of bony density along the lateral border of the internal condyle, either continuous or composed of a string of separate shadows. They usually began at the level of the knee joint. Early cases showed the ossification separated from the condyle and late cases showed it apparently united to the condyle. In the latter group of cases roentgen examination did not disclose whether the condition was a fragment of the condyle or a calcification of the internal lateral ligament. Histologic examination, however, showed the latter to be the case. The authors described a case which suggested that a single trauma might not be necessary to cause this condition but that it might be due to repeated small strains due to faulty weight-bearing and to an associated hypertrophic arthritis.

[ED. NOTE.—Our understanding of Pellegrini-Stieda's disease is different from that of the authors. In this disease as previously described the calcification has been at the attachment of the adductor

21. Ollonqvist, L. J.: Arch. f. klin. Chir. **166**:412, 1931.

22. Rouillard, J., and Bousser, J.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1739 (Nov. 23) 1931.

magnus and not at the internal lateral ligament (see Forty-Sixth Report of Progress). It seems that a distinction should be made between these two conditions.]

Callus Formation and Endocrine Influence.—In discussing his experience in increasing callus formation with thymus and hypophysis extracts, Bergmann [23] said he believed that there was no specific stimulant even though both of these substances increased the amount of callus formed. What was needed was not a substance to increase the amount of callus but a product which would cause the deposition of a small but rapidly ossifying callus. Such an aid had not as yet been discovered.

Sequestrums in the Femoral Head.—Bergmann [24] presented examples of various pathologic entities which had in each instance led to the same result—the formation of a wedge-shaped area of devitalized bone in the head of the femur. In tuberculosis these sequestrums remained attached to the surrounding viable bone and were separated with difficulty. In acute pyogenic inflammatory lesions the sequestrums were rapidly demarcated and loosened. In the aseptic necrosis following traumatism to the hip joint from traumatic dislocation or reduction of congenitally dislocated hips, the sequestrums remained attached to their sites for the most part. They might, however, be freed by trauma later, and become joint mice. Areas of aseptic necrosis appeared in arthritis deformans as well as in osteochondritis dissecans.

Various Forms of Meniscus Cysts.—Mandl [25] pointed out that cysts of the meniscus might be of two sorts. The parameniscal cysts arose from the lateral edge of the cartilage in the region of the capsule where its blood supply was best, and extended from the outer layers of the meniscus into the adjacent capsule. Removal of the meniscus and adjacent involved capsule was advisable. The intrameniscal cyst was quite different. Clinically, it was differentiated from ruptured meniscus only with great difficulty. The cartilage on inspection at operation was generally stained and was the color of ivory. A break was often apparent, and no cyst was visible. However, microscopic examination revealed that there was a cyst which had ruptured and smaller cysts lined with degenerated stroma but without endothelial lining might be demonstrated. In two of twenty-three cases of pathologic menisci, such cysts were found. Removal of the cartilage itself was quite sufficient.

Gangrene of the Extremities in Diabetic Patients.—Escudero and Schultz Ortiz [26] reported fifty-eight cases of gangrene in the extremities

23. Bergmann, E.: Deutsche Ztschr. f. Chir. **233**:302, 1931.
24. Bergmann, E.: Deutsche Ztschr. f. Chir. **233**:252, 1931.
25. Mandl, F.: Deutsche Ztschr. f. Chir. **233**:262, 1931.
26. Escudero, P., and Schultz Ortiz, G.: Semana med. **2**:1914 (Dec. 24) 1931.

of diabetic patients treated in the Hospital Rawson, Buenos Aires; fifty-two were in the lower extremity and six in the upper extremity. The prognosis depended on the evolution and type of gangrene. The best treatment was local prophylaxis combined with medical treatment of the diabetes. In six cases of gangrene cure was obtained by conservative therapy: medical care combined with local physical therapy, rest, baths and exercises. Thirty-five amputations were performed, all in gravely ill patients. Fourteen of them recovered. The authors felt that the site of election in amputation in the lower extremity was the upper third of the lower portion of the leg and the lower third of the thigh since the best blood supply was obtained in these areas.

Method of Determining the Angle of Torsion of the Neck of the Femur.—Rogers [27] described a simple method whereby the torsion (anteversion) of the femoral neck might be determined by fluoroscopy. The patient was laid face down on the fluoroscopic table and the tube centered under the affected hip. The knee was then flexed to a right angle and the thigh slowly rotated outward until the femoral head lay directly in line with the shaft. In coxa valga the head appeared above the trochanter, and in coxa vara it was superimposed on the trochanter but as long as it was in line with the shaft its position upward or downward made no difference. The angle that the lower part of the leg, when flexed, made with the table then gave the angle of torsion of the femoral neck. The author showed by a simple diagram how this conclusion was arrived at.

[ED. NOTE.—The x-rays and fluoroscope are diagnostic aids which are seldom used to their fullest advantage. Any simple elaboration of the usual technic of anteroposterior and lateral and stereoscopic views is worth emphasizing, and an exact method of measuring torsion of the femoral neck should be useful, particularly in dealing with cases of congenital dislocation of the hip.]

Significance of Fat Embolism.—The incidence of fat embolism in subjects coming to medicolegal autopsy was discussed by Vance.[28] An overwhelming percentage of the cases showing fat embolism in the lungs and kidney (the two tissues examined) had received one or more fractures. The author believed that this substantiated the mechanistic theory of fat embolism as postulated by Gauss,[29] and that the true etiologic factor in fat embolism was trauma to fatty tissue. Shock he

27. Rogers, S. P.: J. Bone & Joint Surg. **13**:821 (Oct.) 1931.

28. Vance, B. M.: The Significance of Fat Embolism, Arch. Surg. **23**:426 (Sept.) 1931.

29. Gauss, H.: The Pathology of Fat Embolism, Arch. Surg. **9**:592 (Nov.) 1924.

thought was a condition totally distinct from fat embolism. A large bibliography was given and the present chemical and pathologic findings summarized.

[ED. NOTE.—The forced introduction of liberated fat into patent blood vessels is the most generally accepted explanation of fat embolism today. The relation between shock and fat embolism is not clearly understood, however, and some recent experimental work would tend to show that perhaps fat embolism is one of the phenomena of shock and not the cause of it.[30]]

SURGERY OF BONES, JOINTS AND TENDONS

Incision for Exposure of the Elbow Joint.—Campbell [31] described a new operative approach to the elbow joint, but attributed priority to Mr. W. H. L. Molesworth of Folkestone, England. He claimed that an excellent exposure was obtained and that the approach was less traumatic than others commonly used. Through a median longitudinal incision, after isolation and retraction of the ulnar nerve, the medial epicondyle of the humerus was detached and retracted with its muscular attachments. The joint capsule was then incised and the periosteum with the anterior and posterior capsule may be stripped from the humerus as far as required for exposure. This gave free access to the joint.

Operative Cure of Hallux Valgus and Bunions.—Kleinberg [32] emphasized the importance of adduction of the first metatarsal (metatarsus primum varus) in the causation of hallux valgus. He resected the metatarsocuneiform joint, thus correcting the varus of the metatarsal, and removed the bursa and exostosis at the metatarsophalangeal joint through a second incision. Eight persons so treated had done well.

FRACTURES AND DISLOCATIONS

Treatment of Compound Fractures in Civil Practice.—Creyssel and Armanet [33] reviewed forty cases of compound fracture of the lower portion of the leg. The fractures were divided into three groups and the following conclusions as to treatment were drawn: Group 1 consisted of fractures with small puncture wounds presumably made from within out. The authors found that the general impression that there was little danger of infection was unfortunately not true. If there was any doubt, it was best to do a wide débridement. Some of the indications for débridement were oozing of old blood from the wound,

30. Lehman, E. P., and McNatin, R. F.: Fat Embolism, Arch. Surg. **17**:179 (Aug.) 1928.

31. Campbell, W. C.: Am. J. Surg. **15**:65 (Jan.) 1932.

32. Kleinberg, S.: Am. J. Surg. **15**:75 (Jan.) 1932.

33. Creyssel, J., and Armanet, M.: Rev. de chir. **50**:582 (Oct.) 1931.

edema of the soft parts, absence of diminution of dorsalis pedis pulse. When débridement was not done the puncture wound was never sewed up. Group 2 was composed of fractures with large wounds and injury to the soft part. Amputation was often the only course to pursue. The surgeon should not hesitate to amputate. Amputation permitted hemostasis; it stopped the absorption of toxins from injured tissues and also eliminated the painful and deformed legs which had often been saved with much difficulty only to need a secondary amputation later. Group 3 consisted of fractures intermediate between groups 1 and 2. In this group were those with bone ends protruding from the wound. The bone was considered infected and was thoroughly cleaned. A wide débridement of soft parts was done. The wounds were left wide open and the temptation to plate the bone ends was resisted. Secondary suture and secondary plating were rarely necessary. This group also included those without protrusion of bone ends. Treatment was conservative. Fixation was used only when position could not be maintained with traction or plaster and then in the simplest way possible.

Rare Dislocations of the Foot.—Skrivanek [34] discussed lucidly the mechanism of dislocations of the subastragalar and midtarsal joints. He emphasized the necessity of roentgenograms in two places. Reduction was essential. Subastragalar dislocations could be handled by closed manipulation under general or local anesthesia if seen early enough. However, isolated talonavicular dislocations, with rare exceptions, required open reduction even if seen early. Ultimate function depended in large measure on the amount of initial and surgical trauma. Often, however, an anatomically poor result would function well.

Paravertebral Intramediastinal Hematoma in Fracture of the Vertebra.—Eiselsberg and Gold [35] called attention to the interesting shadows of hematomas in vertebral fracture which could be seen during the first week. These were found in dorsal fractures and fractures as low as the second lumbar vertebra. Frangeheim, in 1928, first described this condition, but aside from observations at postmortem examinations this finding had attracted no clinical attention. Three cases were reproduced by Eiselsberg and Gold. The hematoma was in the paravertebral tissues, was gradually absorbed and might be confused with a tuberculous abscess.

Position of the Head in Intratuberculous Fracture of the Humerus.—Kunz [36] reproduced roentgenograms taken in the ordinary anteroposterior position and contrasted them with pictures taken through the axilla after Iselin's method. The difference was very striking. He

34. Skrivanek, V.: Deutsche Ztschr. f. Chir. **233**:268, 1931.
35. Eiselsberg, A., and Gold, E.: Deutsche Ztschr. f. Chir. **233**:329, 1931.
36. Kunz, H.: Deutsche Ztschr. f. Chir. **233**:441, 1931.

emphasized the necessity of taking the roentgenograms in Iselin's position. Contrary to the accepted view, the head was rotated inward by the subscapularis. The fractured surface faced forward in most cases.

Median Nerve Injuries After Fractures of the Elbow.—Jungbluth [37] felt that palsy of the median nerve in fractures of the elbow was frequently overlooked. The nerve might be completely divided, in which case exposure and suture were indicated, or it might be compressed by swelling in the anticubital fossa, where it lay in a fascial compartment. In the second instance simple incision of this fascial space might suffice.

Periosteum, A Living Bone Suture.—Leadbetter [38] reviewed a series of seventy-six cases of openly reduced fractures of long bones. In the forearm in 82 per cent of the cases that had the bone ends sutured nonunion developed, whereas in only 13 per cent of the cases in which no sutures were used did nonunion occur. The author believed that the quality of the suture was at fault. The tensile strength of sutures were tested after varying lengths of time of immersion in physiologic sodium chloride. Chromic catgut rapidly lost strength. Kangaroo tendon lost strength steadily but less rapidly than catgut. Periosteum maintained its original strength constantly. The tensile strength of periosteum lay between that of no. 2 and no. 3 chromic catgut. After experimentation with rabbits showed that the periosteal suture had osteogenic power (in the preparation of this suture care must be taken to include scrapings from the peripheral layer of cells) the sutures were tried on human cases. Some of the conclusions were: (1) autogenous periosteum had a definite tensile strength which did not vary in contact with body fluids, (2) it was easily obtained, (3) it was definitely osteogenic when properly removed, (4) it proliferated rapidly and early if the bone was poorly immobilized, and (5) mobilization at an early date was possible.

[ED. NOTE.—The editors would question whether the periosteal strip would offer a sufficiently strong suture material in adults in whom the structure often represents a thin membrane.]

Intracapsular Fractures of the Neck of the Femur; Treatment by Internal Fixation.—Smith-Petersen and his co-workers [39] described a new type of flanged nail for use in internal fixation of fractures of the neck of the femur. The advantages claimed for the nail were: (1) absolute fixation of the fragments, permitting early motion of the joint and early weight-bearing, and (2) minimum displacement of bone by the nail with resultant pressure necrosis. The technic, which was minutely

37. Jungbluth, J.: Zentralbl. f. Chir. **58**:3191 (Dec.) 1931.

38. Leadbetter, G. W.: Periosteum: Living Bone Suture, Arch. Surg. **22**:754 (May) 1931.

39. Smith-Petersen, M. N.; Cave, E. F., and Van Gorder, G. W.: Intracapsular Fractures of the Neck of the Femur, Arch. Surg. **23**:715 (Nov.) 1931.

described, consisted in exposure of the fracture through a modification of the anterior (Smith-Petersen) approach which exposed the head and neck of the femur and likewise the greater trochanter, the fragments being nailed and impacted under direct vision. The limb was suspended in light traction postoperatively and weight-bearing was permitted in a short, bivalved plaster spica holding the leg abducted as soon as the patient's general condition permitted, which was usually about three weeks postoperatively. Detailed case reports of the first twenty-four patients treated by this method were given. Twenty of the cases gave the following end-results: bony union, fifteen (75 per cent); nonunion, three (15 per cent), and deaths, two (10 per cent).

[ED. NOTE.—We believe that many surgeons have been disappointed by the results obtained from present methods of treatment in fractures of the neck of the femur. Smith-Petersen and his associates have demonstrated that it is possible to treat these injuries even when in elderly and feeble patients by open reduction with approximately the same mortality as by the closed method. By operation they secure close approximation of the fragments, and solid internal fixation. External fixation is avoided and early function permitted. Under these conditions a high percentage of complete recoveries is obtained. We believe that the method must still be regarded as *sub judice* but that it offers hope of improving on the present results.]

Monocondylar Fracture of the Tibia.—Bistolfi [40] reported fourteen cases of fracture of the tibial condyles, three of the internal condyle and eleven of the external condyle. In this article the author gave an extensive résumé of the previously reported cases, from the Continent, with the various authors' theoretical explanations of the mechanism involved. He stated that various factors existed in each case, namely, partial dislocation of the knee, a rotatory force at time of injury, or the position of the knee in either complete extension or moderate flexion. Because of these variable factors the exact mechanism involved in production of these fractures was not always the same. The author agreed with Wagner, who in 1886 stated that either the internal or the external condyle of the tibia was fractured by compression from the corresponding femoral condyle, depending on the presence of an abducting or adducting force exerted on the extended knee. This explanation fell short when the injury occurred under other conditions. Frequently, in fractures of the external condyle, there were associated ruptures or evulsions of the internal lateral and posterior crucial ligaments of the knee. Various other factors were introduced, such as the tibial spines acting as a fulcrum in the production of the external condylar fractures.

40. Bistolfi, S.: Chir. d. org. di movimento **16**:451 (Oct.) 1931.